PALLIATIVE TREATMENT OF MALIGNANT ESOPHAGOPULMONARY FISTULAS WITH COVERED SELF - EXPANDABLE METALLIC STENTS (SEMS). A SINGLE CENTER EXPERIENCE

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(AbSTRACT): Aim: The aim of our study was to determine the efficiency of SEMSs in patients with esophagopulmonary fistulas, regarding fistula closure, enhancement of dysphagia scores and survival rates. Materials and Methods: Between January 2004 and June 2014, from a total of 133 patients who underwent stent placement procedures, 26 were diagnosed with esophagopulmonary fistulas. In 19 cases the fistulas were caused by esophageal carcinomas and in 7 cases by bronchogenic ones. 16 patients developed aspiration pneumonia, 3 lung abscess and 7 subclinical fistulas. Results: Complete fistula sealing occurred in 26 patients (100%). There were no immediate procedural complications except chest pain in 5 cases. After sealing of the fistulas and antibiotic treatment, pneumonia has regressed. After stent insertion, the dysphagic syndrome improved significantly (mean dysphagia scores decrease from 3.28 to 1.3 after stent insertion). The main goal of palliative therapy in patients with unresectable cancer and esophago-pulmonary fistulas is to close the fistulas, thus preventing the aspiration of saliva and food into the bronchus. Other goals include amelioration of dysphagia symptoms, maintenance of oral intake and improvement of quality of life. Ultimately covered expandable metal stents may increase survival rate as compared with other therapies. Conclusions: The endoscopic placement of covered SEMSs is the treatment of choice for malignant esophago-pulmonary fistulas. Keywords: ESOPHAGO-PULMONARY FISTULAS, SELF-EXPANDABLE METALLIC STENTS (SEMSs).

Patients with esophageal cancers often do not recognize any symptoms until late when the dysphagia is present and more than 75% of the luminal diameter is obstructed. At this time the tumor is often unresectable, either due to invasion of vital adjacent structures, or due to distant metastasis in liver/lungs. Esophago-pulmonary fistulas develop in patients with advanced esophageal and lung cancer and lead to continuous aspiration of saliva or food in the bronchial tree. Their development can be related to tumor invasion, laser treatment, radiation therapy or pressure necrosis caused by a previously placed stent (1).

The goals of palliative therapy in pa-
patients with unresectable cancer aim to ameliorate symptoms of dysphagia, treat complications such as esophago-pulmonary fistula, maintain oral intake, minimize hospitalization, relieve pain, eliminate reflux/regurgitation, prevent aspiration, and of course to improve the quality of life and to increase survival rates (2). There are multiple prospective case series using SEMSs for esophago-pulmonary fistulas reporting occlusion rates of 70-100% and complication rates between 10 and 30% (3).

Self-expanding metal stents (SEMSs) were first introduced for the treatment of esophageal stenosis in the early 1980 and nowadays are gold standard for palliation therapy (4). Esophago-pulmonary fistula is the only condition in which covered expandable metal stents certainly increase survival rates compared with other therapies (5). For persistent fistulas or recurrent fistula, placement of an airway stent may be additional palliative option. Multiple studies evaluate closure rates of fistulas and complications after stent placement. Most of them report complications between 10-30% and occlusion rates between 70-100% (6). Shin et al had a 80% fistulas closure and a mean survival of 3 months (1-56 weeks) significantly longer in patients with complete fistula sealing compared with incomplete fistula closure (15.1 vs. 6.2 weeks, p < 0.05) (7).

**MATERIAL AND METHODS**

Between January 2004 and June 2014 a consecutive series of 133 patients with malignant dysphagia (86.5% men, 13.5% women), aged 46-86 years (mean 61.74 yrs) underwent stent placement under general anesthesia, using fluoroscopic control. Malignancy was established using upper endoscopic examination and biopsy in all patients.

In 84.3% of cases, the etiology of malignant dysphagia was intrinsic, due to esophageal cancer, while in 63.7% of the cases the etiology of malignant dysphagia was extrinsic due compression by bronchial cancer. A total of 26 of the patients with aero-digestive fistulas were identified, ages between 48 and 85 yrs. (mean 60.24 yrs.). In our group 73% of the fistulas were caused by esophageal primary lesion (6 located in upper third, 11 located in middle third, and 1 in lower third of the esophagus) and 27% by bronchogenic carcinomas. At the time of stent placement, 16 patients had aspiration pneumonia and 3 had lung abscesses visible on thoraco-abdominal scan. Seven patients had subclinical fistulas identified during stents placement, not visible on previous CT scan and not manifested clinically. From the 3 patients with lung abscesses, two had esophageal cancer and one had bronchogenic cancer. Only 4 women were diagnosed with fistulas, with a large majority of men. In one case at least 2 fistulas were observed. Only one case was associated with a preinstalled stent, a fistula being noticed close to the proximal opening.

All patients were treated with successfully with a single covered expandable metallic esophageal stents. We used Self-expandable metallic stent (SEMSs) made of a nickel-titanium alloy (Nitinol) with partial polyurethane coverage (20 Ultraflex and 6 Wallflex). We used SEMSs with length between 70-150mm and diameters from 10 mm to 23 mm according to stenotic lesion and position of stricture.

While majority of patients were treated under general anesthesia with tracheal intubation, whenever a major fistula was suspected, we choose in favor of light sedation with topical anesthesia, in order to avoid

ventilation problems generated by the abnormal communication. An upper gastrointestinal endoscopy was performed to establish the upper limit of the esophageal stricture, and a radio-opaque skin marker was placed. Using endoscopic and fluoroscopic help (fig. 1), the guide wire was gently inserted through the esophageal stricture into the stomach. The stent introducer was inserted over the guide wire under fluoroscopic guidance and the stent deployed from the delivery system. In relatively large stenosis the endoscope may be passed and the lower limit marked. Stents are generally selected at least 4 cm longer than the stricture (2 cm above and 2 cm below the stricture). The uncovered portion of the partially covered stents allows for embedding and better anchoring of the stent. Fistula identification relative to stricture was essential, so that the covered part of the stent will cover it and seal the fistula tract.

RESULTS
Stent placement was technically successful in 26 cases (100%), and there were no immediate postprocedural complications, with the exception of moderate chest pain in 5 cases. Complete fistula sealing resulting in resolution of aspiration symptoms (clinical success) was achieved in 26
patients (100%). Before stent placement all patients reported significant dysphagia, with a mean dysphagia score before stent insertion of 3.28. All patients were able to swallow well postprocedural with an overall dysphagia score of 1.3 (tab. I).

**TABLE I**

Dysphagia score was adapted from the Mellow-Pinkas dysphagia score

<table>
<thead>
<tr>
<th>Dysphagia scoring scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to consume a normal diet</td>
</tr>
<tr>
<td>1</td>
<td>Dysphagia with certain solid foods</td>
</tr>
<tr>
<td>2</td>
<td>Able to swallow semi-solid soft foods</td>
</tr>
<tr>
<td>3</td>
<td>Able to swallow liquids only</td>
</tr>
<tr>
<td>4</td>
<td>Unable to swallow saliva (complete dysphagia)</td>
</tr>
</tbody>
</table>

All patients died during the follow-up period (median survival 62.28 days; range 12-137 days) with earlier deaths for those with septic complications (pneumonia or pulmonary abscess). It is very difficult to estimate a benefit in survival, as the life expectancy with an untreated fistula and symptomatic aspiration can be days or weeks. We assume that our patients survived probably longer, but certainly with a better quality of live.

**DISCUSSION**

Esophageal stenting using SEMSs is nowadays the gold standard in the palliation of malignant dysphagia (10). SEMSs are clearly superior to rigid plastic prostheses in the management of unresectable obstructive esophageal cancers, and covered SEMSs are preferred to uncovered SEMS mainly because of lower rates of tumor ingrowth. Multiple complications caused by stent placement in esophageal malignancies have been described, and their frequency range from 10 to 30 % in most series (11). They are related to tumor location and tumor diameter, the presence or absence of the fistula or tumor shelf, use of concomitant chemo radiation (especially radiation which can minimize the tumor diameter), tumor vascularity, and, of course, diameter, length and design of the prosthesis itself. The most typical complications are described in the table below (tab. II).

**TABLE II**

Possible complications of esophageal self-expandable metal stents

<table>
<thead>
<tr>
<th>Procedural Complications</th>
<th>Post-stent Placement Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent misplacement</td>
<td>Halitosis</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Food impaction</td>
</tr>
<tr>
<td>Procedural infection</td>
<td>Over - growth/ In - Growth</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Stent migration</td>
</tr>
<tr>
<td>Tracheobronchial perforation and pneumothorax</td>
<td>Tracheoesophageal fistula</td>
</tr>
<tr>
<td>Bleeding</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux disease / aspiration</td>
</tr>
<tr>
<td></td>
<td>Infection and septic shock</td>
</tr>
</tbody>
</table>

Chest pain is typically observed following stent insertion, in all patients, with an intensity related to the degree of stricture (11). We reported only 5 cases with major

chest pain requiring antalgic medication for more than 24 hours, but we assume thoracic discomfort as a norm in all patients. We do not consider pain a complication unless it prolongs admission and may raise the possibility of subclinical perforation.

Stent migration is the single most important problem related to SEMS. While in some patients it is associated with food impaction due to lack of dietary compliance, in most cases a single factor cannot be pinpointed. Strong esophageal contraction can dislodge a stent, while chemoradiation induced shrinking will make the stent loose. We did not encounter major procedure related complications in our series. While migration is not unusual this was not a significant event in the series. There was one stent migration into the stomach with recurrent dysphagia requiring another stent placement. Endoscopy identified the first stent in the stomach and decided to abandon it as removal can be very difficult and the typical life expectancy of these patients does not warrant a risky retrieval procedure (12). In one case, the tracheo-esophageal fistula was secondary to pressure necrosis by a previously placed stent, so a second stent was deployed inside the first one with excellent result.

The overall results show that SEMSs are very useful for symptom palliation in patients with unresectable or metastatic esophageal cancer and much more so in patients with aero-digestive fistula.

Survival in these cases is very short and without a method for fistula sealing one can expect to survive days or weeks. SEMS are excellent for aero-digestive fistula sealing which is achieved in all patients immediately and the major benefit is in the quality of life.

CONCLUSIONS

Esophagopulmonary fistulas are life-threatening complications, so complete closure of fistulas is the main aim of palliative treatment. The risk of septic shock is higher in patients with lung abscesses. The median survival in our series (~ 62 days) is within the range reported by others (40 to 110 days) but the benefit should not be evaluated in survival per se, but in the quality of life, reflected in the ability to swallow and feed.

Recurrent dysphagia due to overgrowth / in growth tumor is frequently observed in uncovered SEMSs and almost never in partially covered stents. However we recommend to our patients a semi solid diet, followed up by carbonated beverages to avoid food impaction. Usually, recurrent dysphagia is secondary to stent migration in noncompliant patients to regime restrictions.

The endoscopic placement of covered SEMSs is the treatment of choice for malignant esophago-pulmonary fistulas.

ACKNOWLEDGEMENTS

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REFERENCES


A NEW COMPOUND FROM CASSIA AURICULATA WITH ANTI-PROLIFERATIVE EFFECT AGAINST COLON ADENOCARCINOMA

Cassia auriculata (Caesalpinaceae family) is one of the most common Asian medicinal plants. It is used in traditional medicine for the treatment of diabetes, skin problems or eye infections. Extracts from flowers, seeds and leaves possess anti-diabetic, hepatoprotective and emollient effects. A new compound, 4-(4-chlorobenzyl)-2,3,4,5,6,7 hexahydro-7-(2-thoxypyphenyl) benzo[h][1,4,7] triazecin-8(1H)-one, was isolated from the leaf ethanolic extract. After structure elucidation, the compound was tested for its anti-proliferative effect against human colon cancer HCT15 cell line. The MTT assay showed that the cell viability was inhibited by 50% at a dose of 25 µg/mL after 48 h treatment. In addition, the new compound induced apoptosis at 25 and 100 µg/mL as revealed by propidium iodide staining protocol. Lactate dehydrogenase assay confirmed the cytotoxic potential of this compound. The results proved that the new isolated compound from Cassia auriculata leaves possess anti-proliferative effects and it is a promising compound for the treatment of colon adenocarcinoma (Esakkirajan M, Prahbu NM, Arulvasu C, Beulaja M et al. Anti-proliferative effect of a compound isolated from Cassia auriculata against human colon cancer cell line HCT 15. Spectrochim Acta A 2014; 120: 462-466).

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