MINIINVASIVE METHODS FOR PALLIATION OF ESOGASTRIC JUNCTION CANCER

R. HULPUŞ[1], D. SABĂU[2]

[1]PhD candidate "Lucian Blaga" University of Sibiu, [2]"Lucian Blaga" University of Sibiu

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Abstract: *Esophageal gastric junction cancers have a poor prognosis as most of the patients are diagnosed in advanced stages when the disease is incurable. Surgery with radical visa sanction is unnecessary in these cases, even dangerous. The main objective of therapy in these patients is palliative treatment of dysphagia and malnutrition. The idea of miniinvasive techniques should dominate palliative oncology, this article giving an overview of these therapeutic modalities.*

Cuvinte cheie: *carcinom eso-gastric, paliaţie, miniinvazivitate, endoprotezare esofagiană laparo-gastroscopică, foraj transtumoral*

Rezumat: *Neoplaziile joncţiunii eso-gastrice au un prognostic rezervat, majoritatea pacienţilor fiind diagnosticaţi în stadii avansate când boala este incurabilă. Sancţiunea chirurgicală cu viză de radicalitate devine inutilă chiar periculoasă în aceste cazuri. Principalul obiectiv al terapiei acestor bolnavi este de paliaţie a disfagiei şi malnutriţiei. Ideea de miniinvazivitate ar trebui să domine paliaţia oncologică, articolul prezentând o trecere în revistă a acestor modalităţi terapeutice.*

Esophageal-gastric junction adenocarcinoma (EGA) is a neoplastic disease in most cases diagnosed late, when the lesion is advanced and few patients can be treated with radical intent.

Determining the incidence of EGA is difficult to accomplish, this type of cancer being sometimes classified as esophageal cancer, or as gastric cancer, which is not very important in the palliative treatment, its objectives being the same for both types of cancer.(4)

Dysphagia is the cardinal symptom of malignant tumoral esophageal obstructions, which in most cases are caused by esophageal cancer, other causes being the extrinsic compressions given by the mediastinal lymph nodes or by the bronchogenic tumours. In a normal adult, esophagus diameter is approximately of 2.5 cm, a decrease in diameter around 1.3 cm was felt as a difficulty in swallowing solids (table no. 1). At the same time with the discomfort in swallowing, malnutrition also appears.(3) Among the patients with obstructive dysphagia of esophageal tumours, at most 30-40% of them benefit from resection with curative intent.(1,3) Thus, in the patients with unresectable tumours upon diagnosis, the main objective of the therapy is palliation of dysphagia and malnutrition and the prevention of bronchopulmonary aspiration.

Palliation should be considered not as the opposite of the curative therapy, but rather as having its own separate directions, goals and challenges.(2) Its primary purpose must be a substantial improvement in the quality of the remaining life.

The ideal way for the palliative treatment is characterized by a short period of hospitalization, a possible invasive intervention as safe as possible for the patient, less disabling and less painful and a small number of re-interventions.(3,6) Therefore, a rapid and lasting restoration of the ability to swallow and the avoidance of complications are desirable.(4)

Table no. 1. Dysphagia score according to Mellow-Pinkas (14)

Dysphagia score	Symptom
0	No dysphagia
1	Ability to eat some solid food
2	Ability to eat semisolids
3	Ability to swallow liquids only
4	Complete inability to swallow

Many recently developed palliative treatments for patients are now available. These can be divided into endoscopic procedures and non-endoscopic.

Table no. 2. Palliative treatments (4)

Techniques	
Non-endoscopic	Laparo-gastroscopy endoprosthesis Open surgery
	Radiotherapy
	external
	brachytherapy
	Chemotherapy
Endoscopic	Endoscopic prosthesis
	Dilatation
	Laser therapy- Nd:YAG
	Photodynamic therapy
	BICAP bipolar electrocoagulation

Of the palliative treatment methods, choosing the most appropriate one depends on many factors, such as the tumour stage, tumour location, degree of dysphagia, associated diseases,

[1]Corresponding author: Radu Hulpuş, Str. Bacovia, Nr. 22, Sibiu, România, E-mail: hulpusch@yahoo.com, Tel: +40745 162398
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life expectancy, the urgent needs of the neoplastic patient, physician's experience and the team he makes part of (the learning curve).(1,4)

The use of the miniinvasive methods makes the palliative procedure to be easily accepted and tolerated by the patient, with a much higher quality of the remaining life compared to the conventional surgical means. Of the endoscopic palliative methods, the following can be distinguished: dilatation with transient effectiveness, tumour reduction techniques (laser therapy, electrocautery, intratumoral injection with necrotizing agents, brachytherapy) and prosthesis (autoexpandable plastic or metal prostheses). Failure of endoscopic procedures requires the use of other methods to provide nutrition: gastrostomy, which threatened the patient, laparo-gastroscopy endoprosthesis by transtumoral drilling, "rendez vous" endoscopic procedures, open surgery.

Dilatation

References to the impossibility of feeding due to esophageal obstruction occur first in the Ebers papyrus, a text mentioning the forced introduction of food through the mouth, pharynx and esophagus with a bamboo tube.(17) The use of boujie to make esophageal dilatation dates from the XVIth century, Girolamo Fabrizio d'Acquapendente (1537-1619) being cited as the first person to use a special candle to push a foreign esophageal body in the stomach (the word "boujie" comes from the Algerian town Boujiyah, a medieval trade centre selling candles).(18)

The first report of an esophageal dilatation, performed for achalasia belongs to Sir Thomas Willis and dates back more than 300 years, this one accomplishing in 1672 the passing of the esophagus with a carved whalebone whale that has a sponge applied to the distal end.(18,19,20) The dilatation of the malignant stenosis of the esophageal-gastric junction (EGJ) is a simple, fast and cheap manoeuvre that can be done. This is accompanied by an increased risk of esophageal perforation, so that it should be performed under direct visual contact by using a balloon, or under fluoroscopic surveillance by using a guide wire and Savary-Gillard bougies. Due to the limited duration of restoring the esophageal permeability (1-2 weeks), the dilatation should not be performed as an independent therapeutic manoeuvre but as the first step in mounting a stent or in endoscopic tumour ablation.(1,3,6)

Endoprosthesis (transtumoral intubation)

The use of prosthesis for restoring esophageal permeability in case of malignant stenosis is not a new process. For the transtumoral intubation, there are described two methods: pulse intubation (push-through) and intubation under tension (pull-through). Pulse intubation is the most used method, being the first described and consists of a transoral endoscopic introduction of a prosthesis by pushing. Intubation by traction, a method introduced by Mousseau in 1956, involves resorting to laparotomy, involving high gastrotomy for tracking the dilating bougie or the wire guide, the prosthesis advancing as a result of its pulling.

Endoscopic prosthesis

Esophageal prostheses are often the appanage of gastroenterology and gastroenterologist, sometimes assembled by interventional radiologists or by surgery.(12)

Unlike other palliative methods used to treat dysphagia, prosthesis, when successful, has the advantage of giving the patient a chance to be fed orally immediately after a single therapeutic session.(1) The ideal prosthesis should have an internal diameter sufficient to ensure the passage of the food bowel, be flexible and atraumatic, not to migrate and should be repositioned or removed as necessary to allow normal peristalsis, to ensure hemostasis if necessary, to be provided with an antireflux system and to prevent endoluminal tumour invasion.(13)

Rigid esophageal prosthesis

The first report on the use of a prosthesis to maintain esophageal permeability dates from 1845, when Leroy d'Etoilles tried passing a stenosis with an ivory tube.(12) Afterwards, more than 120 years ago, Sir Symonds Charter assembled the first prosthesis for a malignant esophageal stenosis. In the '70s, the Celestin tube was developed, made of latex, which was designed to be placed on open surgery, followed by a plastic rigid Atkinson prosthesis.(13) The assembly of rigid plastic prosthesis is a procedure accompanied by an increased rate of mortality and morbidity, mainly due to perforation and bleeding. For the rigid prosthesis to be mounted, it is necessary, in most of the cases, to perform esophageal dilatation in the first stage.

Although the use of conventional rigid plastic prosthesis in endoscopy was abandoned in the West in the early '90s (1), these implants are still used on a large scale in many parts of the world, the cost of the self-expandable metallic prosthesis being very high.(13)

Self-expanding metal stent (SEMA)

Originally used for the biliary tree (11), SEMS is a prosthesis which is inserted endoscopically, being previously packed, following to be stretched radially once arrived in the desired position, thus restoring esophageal permeability.(1) SEMS has several advantages over the rigid prosthesis, such as the smaller diameter of the mounting system (about 8mm), gradual expansion, greater fully expanded internal diameter, flexibility, stent-in-stent insertion capacity, less post procedural complications.(11) The fact that initially SEMS is packed, it allows its installation without prior expansion, or with minimal expansion, as well as two types of insertion: "proximal release" and "distal release".(1,11)

SEMS was originally made of surgical steel, but nowadays, it is preferred to achieve an alloy of nickel and titanium (nitinol) that provides elasticity to prosthesis, high angular ability, configuration memory, high radial force. Moreover, the nitinol stents allow the patients performing the MRI examination without the possibility of migration. Stent design has changed over the time and includes a wide range of types of prostheses that differ depending on the manufacturer, prostheses with different characteristics (luminal diameter, exerted radial force, flexibility, degree of shortening after installation, braided stents shorten, unlike those unbraid).(13)

SEMS assembly causes immediate resolution of dysphagia (dysphagia grade decreases by 1 or 2 units) (1,11) but it has other numerous disadvantages, such as foreign body sensation (especially in proximal esophageal assemblies), retrosternal pain and obstruction of the tracheobronchial tree. It has been observed over time, that SEMS has a major disadvantage, as they are subject to endoluminal tumor invasion with recurrent dysphagia. Meanwhile, SEMS encrustation at the level of the esophageal wall makes the repositioning or the removal not to be possible to be performed.

To avoid this inconvenience, coated stents were introduced. But in the latter, it was found that reducing stent fixation to the esophageal wall, prosthesis migration occurs more often. Thus, it has imagined a new type of SEMS that presents the characteristics of both covered and uncovered ones – an external nitinol network that ensures the proper fixation of the prosthesis to the esophageal wall and an inner layer of polyurethane prevents tumour endoluminal invasion of the prosthesis (stent-in-stent design).(1,13)

Another inconvenience that may occur after installing the SEMS is recurrent dysphagia caused by mucosal hyper proliferation located at the ends of the prosthesis. The new stents

often have the edges fully covered to prevent granulation tissue by reducing tissue irritation.(1)

Mounting stents for distal esophageal tumours and EGJ represents a particular problem. Compared to those for the medium esophageal tumours (proximal esophageal tumours are difficult to be endoscopically provided with prosthesis), which provides a lower palliative treatment and are associated to higher risks of complications. Because the distal portion of the stent is free in the gastric fundus and cannot be fixed to the wall, it can erode the posterior wall of the stomach, causing ulcers and bleeding. Also, a stent passing through EGJ cannot remain straight due to the normal anatomical angle between the esophagus and cardia, resulting in the same aforementioned complications. Stents angulation may explain the finding that improving dysphagia is lower than in the case of the proximal stents.(4) The patients with stents assembled at the level of EGJ often have the symptoms of gastric reflux and of oesophagitis with the installation of aspiration pneumonia in 20 to 70% of cases, which spurred the creation of SMA with antireflux valves. Also, SMA mounted at the level of EGJ are associated with a higher rate of migration, the prosthesis with proximal flange diameter greater being preferred.(11)

Self-expandable plastic stent (SEPS)

Self-expandable plastic prostheses were designed as an alternative to SEMS having the advantage of being easily extracted and more affordable. Palliation provided by SEPS is similar to the SEMS, but considering the larger diameter of the mounting system, these one have a higher rate of technical failure. SEPS can be reused more easily than SEMS, being initially used to treat SEMS by successive dilatations of the benign esophageal stenosis.(11)

Intratumoral injection therapy

Intratumoral injection therapy was performed with a variety of chemicals, chemotherapy and sclerosing agents such as ethanol, cisplatin, morrhuate sodium, polidocanol. It is an inexpensive, easy to perform method, suitable for the small proliferating tumours. Alcohol injections have proven to be effective in eliminating dysphagia in 80% of cases, with results comparable to laser therapy. The method can be used for tumour endoluminal invasion of the prosthesis. However, this procedure is rarely used because of the many drawbacks: the lack of standardization, it is difficult to appreciate the depth of injuries, late effects and multiple therapeutic alternatives.(1,11)

Endoscopic bipolar electrocauterisation – BICAP

The principle of the method consists of the use of the thermal energy for tumour ablation, provided by electrodes attached (hemi) circumferentially to an olive connected to a flexible catheter introduced endoscopically. Due to tissue coagulation produced, it is indicated in the circumferential esophageal tumours, and not in the case in the sinuous, asymmetric, un-circumferential tumours. The success rate in the treatment of dysphagia varies between 80% and 90%, generally requiring 1, 2 therapeutic sessions. Procedure complications include: perforation, bleeding and post procedural secondary stenosis.(6,11,15)

Laser therapy Nd:YAG

This therapy involves applying a laser beam for tissue thermal ablation by coagulation necrosis and vaporization. The main indication is the exofitic tumours smaller than 5 cm, the infiltrative tumours are contraindicated due to the risk of perforation. As a result of the temporary effect of improving dysphagia, it is necessary to repeat the laser therapy 4-6 weeks later. The complications of bipolar electrocoagulation versus laser ablation are similar.(1,3,6,11,15)

Photodynamic therapy

Photodynamic therapy (PDT) causes the destruction of the tumour tissue using a monochromatic light source with a specific wavelength that is activated in the presence of oxygen, a photosensitizing agent administered previously, agent that is captured by the tumour tissue.(7) PDT has two stages: in the first stage, the photo-sensitizing chemical precursor in the biosynthesis of the hem is introduced systemically (orally or intravenously) being accumulated in the neoformation tissue, knowing that the rate of synthesis of porphyrins is significantly increased in the dysplastic and neoplastic cells (10-fold than in the normal cells).(8,10) In the second stage, the sensitized tissue illuminated with a light of a selected wavelength (depending on the photosensitizing substance), activates the photosensitizing agent that reacts with the cell membrane forming ionic radicals that interact further with oxygen to produce cytotoxic oxygen molecules, known for more than 100 years due to the research made on ozone and active oxygen.(8,9)

Clinical experience in EGJ palliative neoplasms have only a few centres in Europe, USA and Canada (7), the literature describing palliative PDT as a method particularly suitable to polar esophageal tumours (cervical esophagus, distal third).(8) In addition to the high costs, there are many complications that limit the method to be applied to the patients who could benefit from this procedure, the most common being prolonged skin photosensitivity, which requires avoiding sunlight for 4-6 weeks.(3,7) Another inconvenient is a major need for re-treatment after 8 weeks.(7,11)

Argon plasma electrocoagulation APE

Argon plasma electrocoagulation (APE) consists in applying thermal energy to tissues causing superficial lesions of 2-3 mm, being a process that can be applied to large tissue areas. Energy is transferred from a monopolar probe through an ionized argon gas environment. The lesion depth raised controversy in relation to the usefulness of the treatment of esophageal exofitic cancer, varying according to the energy level used (56 - 90W). However, PDT and laser therapy produce deeper lesions, but APE is much cheaper, more accessible and easier to perform. As in the case of laser therapy, APE can be used for endoluminal tumour invasion of stents. Although it is a non-contact therapeutic method relatively safe and effective, it has the disadvantage of the need for re-interventions in about 3-4 weeks, and complications including: pneumatosis, pneumoperitoneum, subcutaneous emphysema, pain, ulceration, stenosis, bleeding, perforation and even death can occur.(1,3,11,15)

Laparo-gastroscopic esophageal endoprosthesis by transtumoral/transstenotic drilling

The idea of mini-invasiness should dominate palliative oncology. So, methods have been created and perfected to replace the traditional gastrostomy definitive, endoscopic palliative method, a mini-invasive and invalid procedure. Unfortunately, these endoscopic methods are limited due to the technical difficulties related to the endoscopic approach, viewing, placement, catheter failure (esophageal poles are localisations to which the endoscopists are reluctant, major strictures, filiform lumen) and propulsion (propulsion assembly by elastic pusher). Firm haulage, the possibility of catheterisation of filiform lumens of 1-2 mm, sometimes anfractuous, distal visibility, visual tracking of prosthesis placement or expansion, visceral or parietal metastasis intraoperative evaluation represent the advantages of laparoscopy, which allow the extension of gastroenterology and oncology indications of stenting.(17)

Laparo-gastroscopic esophageal endoprosthesis by transtumoral drilling is a mini-invasive procedure of esophageal

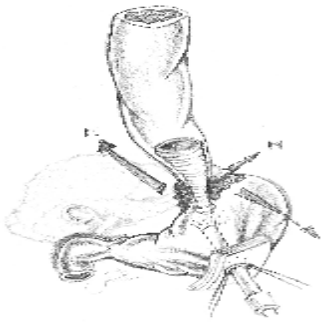
prosthesis by laparogastroscopic approach recognized nationally and internationally, presented in 2005 within the sixth Congress of gastric cancer in Yokohama, when it was also awarded the Grand Prix. The process consists in fitting a prosthesis, either of plastic (preferred due to cost price, compressive hemostatic application in case of hemorrhage secondary to transtumoral drilling, reduced risk of endoluminal tumour invasion of prosthesis) or of flexo-metallic, self-expandable "proximal" or "distal release" by traction and not by pushing. The fact that the installation is accomplished by traction allows the progressive expansion by guiding the transtumoral drilling and the modulation of the traction force depending on the resistance encountered. The "rendez-vous" endoscopico-laparoscopic option is ideal for the prosthetic fitting (golden standard).

The prior or pre-surgical assembly of an oro-gastric probe simplifies the process, representing actually the "key" to success.

Pneumoperitoneum is installed, and the telescope is inserted exploring the peritoneal cavity thereby realizing the most accurate staging (detecting the visceral or peritoneal metastasis escaping the preoperative investigations). Afterwards, the stomach is brought to the anterior abdominal wall, practicing an approach gastrotomy through which the telescope is inserted into the stomach. It explores the gastric cavity being also able to highlight the tumour biopsy, as well as the retrograde catheterization of the cardia with probes with or without mandren, if the anterograde (oral) catheterization is not possible. Once the esophageal catheterization performed, cardia is expanded with probes progressively increasing diameters. The assembly by traction of the prosthesis follows, its oral insertion and the videoscopic control of its positioning, by direct visualization with the telescope inserted into the stomach. The endoscopic control is possible and desirable in all cases, the "rendez-vous" techniques represent the variant of choice, bipolarity visualization significantly reducing the length of the surgery.

Laparo-gastroscopic esophageal endoprostesis, although it is performed under general anesthesia, is a short-term intervention (between 20 to 100 minutes, on average 40 ± 2 min) and the surgical aggression, both parietal and visceral is minimal. In fact, both the length of the intervention and its technical success depend on the ability and speed of probe placement (often with mandren) of trans-tumor filiform drilling. It is a simple, fast and efficient procedure, which saves the patient from gastrostomy and allows the normal oral feeding, the patient being able to eat 8 to 12 hours after the surgery (progressively, liquids, semisolid and solid food and the hospitalization length is short, ranging from 3 to 7 days, due to gastroraffia, drain tube and process novelty.(16)

Figure no. 1. Laparo-gastroscopic esophageal endoprosthesis by transtumoral drilling for an eso-gastric junction cancer with multiple metastatic determinations (collection Prof. Dr. Dan Sabău)



Conclusions:

Most patients with eso-gastric adenoma are diagnosed in advanced stages, the disease being incurable. Dysphagia is the cardinal symptom in EGJ cancer; difficulty in swallowing the food has already depressed the patient, emotionally affected in the presence of a merciless disease. Moreover, malnutrition due to dysphagia accelerates the physical and mental deterioration. The removal of esophagus is preferred in the benign postcaustic stenosis and compulsory in operable esophageal cancer stage, but it becomes useless and dangerous in esophageal cancer exceeded.(16)

Palliation should be defined as the sum of all care services awarded to the patients who do not benefit from curative treatment. Its main purpose is to improve the patient's quality of life and not necessarily of life length.

Stenting remains the method of choice and the most often used in palliative dysphagia of malign cause, being a well tolerated procedure, initially effective in relieving the symptoms of obstruction in about 98% of cases, although the number of patients who subsequently developed recurrent obstructive symptoms approaching 20%.(2) Endoscopic prosthesis fails in about 20-30% of cases due to the technical impossibility of crossing the tumour stenosis with the endoscope or due to the endoscopist's hold-backs in the case of "sensitive" areas (poles of the esophagus), establishing itself as a method of palliative dysphagia in the detriment of the invalid gastrostromy.

Choosing the appropriate stent should be individualized based on patient's characteristics, tumour type, location, prognostic and the therapeutic plan.(12) New technologies in stents include the use of biodegradable materials in their manufacturing, covered by a layer of radioactive stents, pharmaco-active stents. The biodegradable stents are currently used for benign stenosis, but a possible use is the treatment of dysphagia in patients undergoing chemotherapy. Including radioactive or cytotoxic agents could increase the efficiency, particularly in preventing endoluminal tumour invasion at the both ends of the stent. In the case of canine experimental models, the radioactive stents caused fibrosis and impaired the esophageal wall, but major complications such as perforation or fistula were not observed.

The effectiveness of these stents remains to be evaluated in clinical experiments.(4,11) In the patients with a diagnosis of inoperable oncology, in whom the endoscopic stenting is contraindicated due to technical criteria, palliation through minimally invasive approach may be preferred.

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