Thesis of PhD dissertation

Surgical palliation of malignant mediastinal tumors

Dr. Imre Tóth

Semmelweis Ignác Teaching Hospital, Miskolc, Hungary
Department of General and Thoracic Surgery

Head of Doctoral School:
Prof. Dr. Sámuel Komoly

Head of Doctoral Program:
Prof. Dr. Péter Örs Horváth

Supervisor:
Prof. Dr. Tamás F. Molnár

Clinical Tutor:
Dr. Géza Szűcs Ph.D.

University of Pécs
Faculty of Medicine

Pécs
2013

1. INTRODUCTION

The mediastinum is a hard-to-reach place for surgical intervention. To operate on the mediastinum is always a challenge for the surgeon. Numerous primary and secondary malignant tumors can occur here. The compression of the great vessels or the cardiac atrium causes global circulatory insufficiency. The functional loss of the esophagus is also life threatening. The describing of the mediastinal surgery – and also the mediastinal palliation – remains inevitably incomplete in this study because "the most frequent case is the rarity" in this region.

2. OBJECTIVES

The aim of the study was to analyze the role of palliative mediastinal surgical methods in the light of modern thoracic surgical methods, their completion with our own procedures and retrospective introduction of the achieved results. The historical background was emphasized to show the development of methods.

1) The subxyphoideal pericardial fenestration is connected in the literature to the name of the French baron *Larrey* who was *Napoleon*'s military surgeon. Does he really have the priority?
2) The role of the thoracic surgical methods as a part of the complex therapeutical modalities in the diagnosis and therapy of the upper mediastinal masses are changing. What is the role in the nowadays oncoteam guided interdisciplinary collaboration of the collar (*Carlens*) and the parasternal mediastinoscopy (*Chamberlain Stemmer*)?
3) What are the possibilities of surgical treatment of malignant pericardial effusions in a medical care unit without heart surgery background?
4) What kind of technical modifications can simplify the surgical palliation of malignant pericardial effusion and how can its efficiency be improved?
5) Can the cost-effectiveness be improved in the surgical palliation of advanced malignant esophageal strictures without decreasing the quality, and where are the boundaries of it?

3. SOURCES AND METHODS

3.1. Palliative care, surgical palliation

The WHO definition of palliative care is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." According to Webster's Medical Dictionary, "Medical or comfort care that reduces the severity of a disease or slows its progress rather than providing a cure." The word "palliata" in Latin means "to hide".
I will define as surgical palliation of mediastinal tumors hereinafter the following interventions:

1. that is performed on advanced-stage cancer patients in whom there is no chance of full recovery;
2. that is performed on malignant cancer patients in whom a curative intervention is not possible because of the risk due to their co-morbidities;
3. radical surgical removal of the tumor was not possible or it was not successful (R1, R2 resections);
4. the primary objective of it is to improve the quality of life
5. the secondary objective of it is to prolong life compared with untreated cases, enabling the application of other types of (oncological) palliative (chemo-, radio-, immuno) therapy

3.2. Patients

The central computer database of Semmelweis Medical Center and University Teaching Hospital has contained detailed information since 1st January 2005. A list of the computer database was created about the specifically screened patients based on appropriate ICD and / or WHO codes. The database on upper mediastinal tumorous patients included a 5-year period between 2007 and 2011. We had a previous five-year database covering our patients with pericardial effusion since 1st January 2000, so in the case of pericardial effusion 10 years worth of material could be analyzed. More than three years of material was available regarding patients palliated with self expandable stent, covering the period from 2008 September until 31st December 2011. The staging was done based on the 6th edition of TNM.
In the case of the upper mediastinal tumors, the vast majority of our activity was diagnostic operations.
In the case of advanced esophageal cancer altogether 6 R1 and 3 R2 resections occurred. Three of them had to be excluded from the study. The mean survival of the remaining 6 incomplete resection cases did not differ from that of all resected cases. This was the reason why the data on resections in stage III.-IV. cases was not excluded from the study for the sake of comparison with the other palliative methods, although R0 resections are considered as curative by definition.

3.3. Statistical analysis

The statistical analysis was performed in the Department of Applied Mathematics, University of Miskolc. We used Microsoft Excell Tables and the "Statistica 11.0" software package (Stat Soft Inc. USA). The result was controlled with the "Matlab R2010b" software package (MathWorks Inc. USA). This calculation also shows the lower and upper confidence bounds for the cumulative distribution of survival that were calculated using Greenwood's formula. The comparison of survivals was analyzed with Student's two-sample t-test. The critical value of "t" was given at a level of 95% (significance level: $p<0.05$) with n_1+n_2-2 degrees of freedom and was compared with the calculated "t" value. Those data which were easily comparable were shown in histograms. The effect of co-morbidities to the survival was proved with the Cochran-Mantel-Haenszel's logrank test. The histograms and the logrank test were calculated with the Matlab software.

4. PALLIATIVE SURGICAL ACTIVITY IN THE MEDIASTINUM

4.1. UPPER MEDIASTINAL MALIGNANT TUMORS

4.1.1. Historical background

The method of scalenus biopsy was published by *Daniels* in 1949. *Harken* and his colleagues developed *Daniel*'s method and they performed unilateral mediastinoscopy using laryngoscope. The suprasternal approach of the mediastinum was written down by *Radner* in 1955. The method of collar mediastinoscopy was published by *Carlens* in 1959. In Hungary, "behind the Iron Curtain" *Matus* and *Schnitzler* from the University of Debrecen performed the first collar mediastinoscopy 3 years after *Carlens*'s publication. They published their first results in 1964.
McNeil and *Chamberlain* published the method of anterior mediastinotomy in 1966. This approach gave new impulse in the development of mediastinal minimalinvasive diagnostics. Five year later, in 1971 *Stemmer* presented his method of parasternal mediastinoscopy. In Hungary *Besznyák* and *Nemes* used this technik in the early 70s.
The superior mediastinum can be entirely examined with the help of the combination of collar and parasternal mediastinoscopy. Nowadays, a series of publications can be read about the benefits and

results of re-mediastinoscopy in cases of neoadjuvant oncological therapy patients. In this field and in the field of combined extended mediastinoscopy, *Rami-Porta* had pioneering activity.
The extended mediastinoscopy with a distally guided long device was called *Specht* kind of extension, but in the book of *Surgical Operations* two authors, *Akovbianitz* and *Bartel* were mentioned as the first by *Keszler*.
The idea of an extended meaning for mediastinoscopy was first raised in the publication of *Ginsberg*. Today, the role of TEMLA (transcervical extended mediastinal lymphadenectomy) and VAMLA (video-assisted mediastinoscopic lymphadenectomy) has been discussed by European authors as *Hürtgen, Leschber* and *Zielinski*.
We have performed collar mediastinoscopy as staging and diagnostics for decades in our department. The founder and head of our department, *Prof. János István Kiss*, was a colleague of *Matus* at the University of Debrecen, so he studied this method firsthand. The video-medoastinoscopy was introduced in our department three years ago. We use the parasternal mediastinoscopy approach not only for diagnostics, but in certain cases for creating pericardio-pleural shunts, as well.

4.1.2. Our own activity in the upper mediastinum

4.1.2.1. Materials and methods

We analyzed retrospectively the data of our patients operated on with a diagnosis of mediastinal tumor in a 5-year period from 1st January 2007 till 31st December 2011. We found altogether 80 such patients. In the knowledge of final histological examination 32 of them were excluded from the study due to benign disease.
The follow-up was closed on 31st August 2012.

4.1.2.2. Results

The gender ratio was 24 females and 24 males. The mean age was 51.61 years (max. 78, min. 24, SD:15.35).
26 Stemmer mediastinoscopies, 16 Carlens mediastinoscopies, 5 thoracotomies and 1 VATS for malignant mediastinal tumor were performed in the examined period.
The 58.3 % (27/48) of patients had some kind of complaints and 21 patients were detected by screening. 12 patients (25%) had not got any co-morbidity and had negative anamnesis.
The examined patients were divided into groups as haematological tumors 27% (13/48) (Hodgkin, Non-Hodgkin lymphomas), non-small-cell lung cancer metastasis 27% (13/48) (squamous cell carcinoma and adenocarcinoma) and neuroendocrine carcinomas 23% (11/48) (small cell lung cancer and malignant carcinoid). These 3 groups contained three-quarters of all cases. The remaining quarter of patients' diseases were so inhomogeneous (breast cancer metastasis, thyroid gland carcinoma, sarcomas, thymus tumor, germ cell tumor, large bowel carcinoma metastasis) that there was no point in using them as a fourth group in the comparisons.
Complications were observed in 8 cases (16.6%) (pneumothorax 1, bleeding 1, suppuration 2, embolism 1, respiratory insufficiency 2).
Compression symptoms were caused by the tumor in 24 patients (50%) and in 9 cases (18.75%) it was superior vena cava syndrome.
The average extent of tumors was 74.55 mm (min. 30, max. 200, SD 34.92) and in 14 cases it was multifocal.
The postoperative mortality rate (within 30 days) was 16.6% (8/48) and the hospital mortality rate (within 2 weeks) was 4.16% (2/48).

Each surviving patient underwent oncological treatment (33/40, 82.5%). 22 of them were responders (66.6%) and in 11 patients complete remission was detected (10 hematological malignancy and 1 breast cancer metastasis).
At the time of the closure of follow-up, 12 patients were alive (25%), and in 6 cases only the last hospital appearance was known; the exact survival was unknown. Thus, the mean survival was 614.7 days (min. 5, max. 2040, SD 89.59).
According to the statistical analysis the best survival was in the hematological malignancy group, and the difference was significant compared with the other two groups.

4.1.2.3. Discussion

The role of abdominal surgical staging markedly decreased in the PET-CT era.
However, in the field of the diagnostics of mediastinal masses the role of surgery is still important.
In the case of lymphomas, the large size and mass in the mediastinum causes compression of different adjacent structures. In about in 8 % of all lymphoma patients vena cava superior syndrome (VCS) occurs, and in about 2-10% of VCS cases the origin is some kind of lymphoma. There were 24 patients with some kind of compression in our study, and 9 of them were VCS. The origin of VCS were lymphoma in almost half of cases (4/9, 44.44%). Even one-third of all patients with compression syndrome had lymphoma (8/24, 33.33%).
Nevertheless, 65-80% of VCS is caused by mediastinal metastasis of pulmonary cancer, based on the literature. VCS occurs in 3% of all lung cancer cases. The rate of neuroendocrine lung cancer mediastinal metastasis (small-cell and malignant carcinoid) is high in our study (11/48, 23%). Half of our all patients were operated on for lung cancer metastasis (24/48, 50%).
As shown by survival data, in the case of lymphomas chemotherapy or the "target" immuno-chemotherapy is very effective (mean: 1104 days, SD: 404).
The most effective palliation is the tumor reduction or debulking in case of upper mediastinal masses with consequent compression syndromes. The mediastinal carcinoid (thymus carcinoid) does not respond to radiotherapy, so its removal is the only choice. In case of thymus carcinoma the removal of it with subsequent chemo- and radiotherapy could extend the life of patient.
We performed three "heroic" resections for extended malignant mediastinal mass in our five-year material. All patients were relatively young males. All of them survived several months and one of then is still alive.

4.1.3. Conclusions

- Most surgical interventions for upper mediastinal masses are diagnostic operations as part of complex palliative treatment (mediastinoscopy – collar/parasternal).
- Half of these operations have to be performed for mediastinal metastases of lung cancer; one quarter of them are for hematologic diseases and the rest are for various tumors.
- More than half of the upper mediastinal masses cause manifest compression syndromes.
- The role of surgical methods in the diagnosis of hematologic malignancies is still essential.
- Primary resection is indicated in case of large-sized mediastinal masses, especially in case of sarcomas, due to the lack of other effective therapeutic modalities.

4.2. THE TUMORS OF PERICARDIUM AND EPICARDIUM AND THE MALIGNANT PERICARDIAL EFFUSION

4.2.1. Historical background

The French surgeon *Ambroise Pare* observed in the sixteenth century that in some cases of stab wounds in the heart region the agony is longer before death occurs. The physiology and pathology of cardiac tamponade was clarified a century later by the British physician *Richard Lower*. The first successful myocardial suture was performed by *Ludwig Rehn* (1896).

Received wisdom teaches us that the first pericardiotomy was performed by *Baron Dominique Jean Larrey*, *Napoleon*'s chief military surgeon, on 18th March 1810. The priority debate is not influenced by the sad fact that the patient died some days after. *Larrey*'s original incision was made parallel to the upper edge of the sixth rib under the left nipple.

In 1824, a 22-year-old soldier was taken to the hospital. He suffered a thumb-sized stab wound to the left chest, in the region of the xyphoid cartilage. Later, *Larrey* removed the bandage and three bottles of wine-colored fluid exited the wound. The more fluid evacuated, the more the patient was relieved. After this successful case, *Larrey* looked for a technique for pericardiotomy. He examined cadavers, putting a knife into the corpse at the same point and following the same direction as in the case of the recovered solder's wound. *Larrey* published his new method for pericardiotomy in 1829.

There is a lesser known surgeon during *Larrey*'s time, named *Francisco Romero*, who was born in Catalonia. He became a surgeon at the Royal College of Barcelona. His first patient with pericardial effusion was a 35-year-old farmer he treated in 1801. *Romero* made the incision next to the curvature of the sixth rib at the cartilage level. His first patient recovered in four months. *Francisco Romero* presented his memoir, describing his technique of open drainage of thoracic effusions on 13th April 1815 in Latin.

Comparing the dates, it is clear that *Francisco Romero* has a priority of 14 years before *Larrey*'s publication.

Almost 100 years later *Sauerbruch* worked out the method of longitudinal pericardiotomy for purulent pericarditis, and he performed an operation for constrictive pericarditis (1913).

In 1957 *Effler* and *Proudfit* published their experiences of 16 pericardial biopsies using parasternal approach without opening the pleural cavity. The technique of percutaneous pericardiocentesis was described by *Frank Schuh* in 1840. The first publication on using a polyethylene catheter in pericardial paracentesis was reported in 1955. The method of parasternal mediastinoscopy was published by *Stemmer* in 1971. In the same year his co-author *Calvin* reported the results of 152 parasternal mediastinoscopies. In two of these cases a pericardium fenestration was performed using this approach.

The method of modern subxyphoideal fenestration was first published by *Fontenelle* in 1970. (The direction of this procedure is similar to the *Larrey* approach.)

A further milestone in the history of managing pericardial effusion was the appearance of thoracoscopy, later videothoracoscopy. The first direct pericardioscopy was performed in 1986 by *Little*. He chose the *Larrey-Fontanelle* (subxyhoideal) approach and used a rigid (*Goldberg*) mediastinoscope. The first description of a pericardioscopy with a flexible device (choledochoscope) was published by *Wong* in 1987. Perhaps one of the first publications on thoracoscopic pericardial fenestration was *Ozuner*'s in 1992.

An alternative approach for the management of pericardial effusion was the creation of the pericardio-peritoneal shunt. It was developed in 1990 for the treatment of recurrent malignant pericardial fluid.

The first report of VATS pericardium fenestration was published by *Michael J. Mack* in 1993.

The first publication in connection with the treatment of pericardial effusion was written in the Ferencz József University of Sciences, Szeged by *Professor Emil Troján*. In a case report from the University of Debrecen, *Kónya* introduced a so-called pericardiotomia inferior operation and drainage for purulent pericarditis in 1968, two years before *Fontenelle*'s article.

Besznyák and *Nemes* reported 15 cases of parasternal mediastinotomy in 1976. One of these operations was for pericardial effusion. *Lajos Tamás* from the State University of New York (son of a gynecology professor from Pécs) described the technique of percutaneous drain pericardioscopy.
The life-work of *Károly Vincze* from the Kaposvár County Hospital was prominent and outstanding regarding treatment of pericardial effusion. His first case report on this theme was published in 1977. He applied the *Fontenelle*-type subxyphoideal approach with modification. This method could be performed with local anaesthesia and without resection of the xyphoid process. Later, he applied lighting retractor and he performed the first endoscopic pericardial fenestration in Hungary.
The problem of recurrence and persisting malignant pericardial effusion led *Tamás F. Molnár* (Frenchay Hospital, Bristol) to the idea of developing the technique of creating a direct pericardio-peritoneal shunt. Later, at the University of Pécs, he improved his method using laparoscopic and VATS techniques.

4.2.2.1. Introduction

The number of patients with secondary malignant pericardial effusion is steadily increasing due to the improving efficacy of complex cancer treatment modalities. The incidence of malignancy associated with pericardial involvement ranges from 8 to 20% in other autopsy studies. The tumorous infiltration or carcinosis of the pericardium could cause pericardial effusion in up to one-third of cases of malignancy, thus potentially interfering with the otherwise desirable oncological treatment.
The existing surgical methods for the management of pericardial fluid are well-established but are not without limitations. Pericardiocentesis and the Larrey-Fontenelle approaches using a subxyphoideal fenestration have a recurrence rate ranging between 43 and 69% after pericardiocentesis and 9 and 16% after pericardial drainage. The video-assisted thoracoscopic surgical (VATS) pericardio-pleural fenestration requires anaesthesia with contralateral single-lung ventilation. The transdiaphragmatic pericardial fenestration was developed as an alternative method, but the pericardio-peritoneal window might be blocked by the adjacent abdominal structures. Having extensive experience in collar mediastinoscopy, we utilized the existing armamentarium of the Carlens procedure in a Chamberlain approach in order to achieve pericardial decompression in the form of a pericardiopleural window. As we described in the historical chapter there are antecedents of our idea of mediastinoscope-controlled parasternal pericardial fenestration (MCPF) using a similar approach or similar armamentarium. However this type of operation has been unknown in the literature as a standard intervention.

4.2.2.2. Patients

From January 2000 to December 2009, 22 cases out of the 73 consecutive patients with pericardial fluid that we treated were operated on with the mediastinoscope-controlled parasternal pericardial fenestration (MCPF) (*Table I.*).

Table I.: Interventions for pericardial effusion

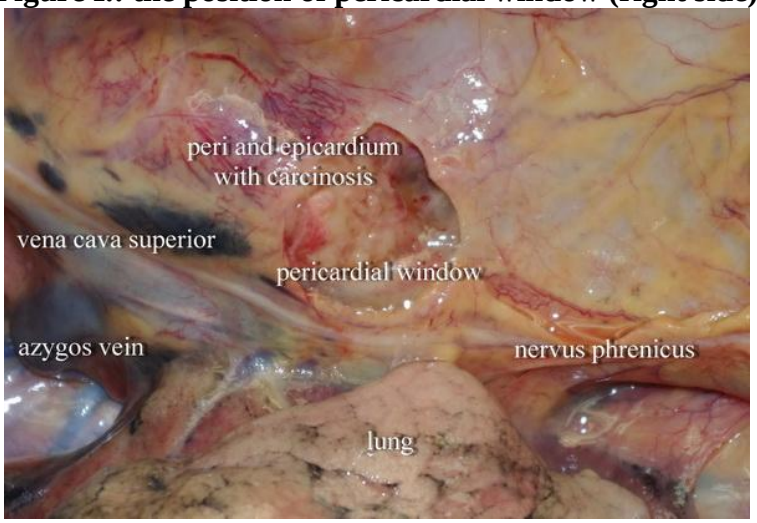
Number of patients: 73
Malignant pericardial effusion: 35
Pericardiocentesis+drain (percutan drainage): 23
Subxyphoideal fenestration: 23
Parasternal fenestration (MCPF): 22
Transdiaphragmatic fenestration: 2
VATS pericardial fenestration: 2
Thoracotomy with fenestration: 1

In the first half of the examined period the low risk patients were selected in order to avoid complications. Since the method was novel, the decision depended on the performing surgeon. In the second half of the examined period the MCPF was performed almost exclusively in all cases of malignant pericardial effusion.
Exact survival data was available in 14 cases. We closed the follow up on 31st May 2011. At that time two of our patients were alive, so their survival data were censored in the statistical analysis.

4.2.2.3. Method: the technique of mediastinoscope-controlled parasternal pericardial fenestration (MCPF)

The patient was placed in a 10-30 degree supine Fowler position. Anaesthesia was introduced with a single lumen endotracheal tube. A transverse skin incision was made above the sternal end of the third or fourth rib, a little bit longer than the expected length of its cartilaginous part. The laterality of approach (i.e. left or right) was decided based upon the pleural involvement, as tumor-free pericardiopleural reflection is required. A left-sided approach was preferred when both pleural cavities were suitable for the procedure. After blind splitting the pectoral muscles the sternal edge of the rib was resected. The internal thoracic artery and vein were identified and secured. The pleural cavity was opened close to its mediastinal reflection. A limited exploration of the thoracic cavity was undertaken introducing a rigid mediastinoscope. Keeping aside the lung with a long retractor a holding stitch secured pericardial access ventrally to the phrenic nerve. Lifting up this stitch, a window of at least 3 cm in diameter was created on the pericardium using scissors to manipulate within or parallel to the main tube of the mediastinscope (Figure I.).

Figure I.: the position of pericardial window (right side)



Introducing the mediastinoscope into the pericardial sac, it was possible to perform a limited pericardioscopy. Then a silicone chest tube was inserted into the pleural cavity. The chest tube is removed 48-72 hours after the intervention depending on the chest X-ray finding.

4.2.2.4. Results

12 female and 10 male with average age of 57 years (min. 26, max. 72, SD 11) underwent MCPF.
There were no operative deaths in the group of 22 MPF patients. Transient intraoperative dysrhythmia was detected in 3 cases (14%). We lost one patient (4.5%) in the postoperative hospital stay due to a cascade of inflammations. Two of these patients are still alive one and a half years after the end of the

examined 10-year period. All of the surviving patients had a minimum of 2 months of symptom-free survival. The mean survival was 390 days (SD 413). The difference is remarkable and significant in the survival between the patients with lung cancer origin (174 days, SD 153) and those with breast cancer origin (601 days, SD 473).
Based on our results it is remarkable that the number of long time surviving patients is relatively high in spite of the tumorous infiltration of the pericardium or the heart.

4.2.2.5. Discussion

Even 20 years ago the most frequent reason of pericardial effusion was some kind of metabolic disease, mainly uremic polyserositis. Nowadays, the first place is of malignant origin.
The observation about the frequent recurrence of malignant pericardial effusions made the development of a new method necessary. The result of this development was the preparing of a pericardio-pleural shunt from parasternal approach. Unfortunately, the idea presented is not exclusively new. However our PubMed search was unable to reveal any publication that discussed an application of parasternal pericardial fenestration in cases of neoplastic pericardial effusion.
According to the literature the best palliation for malignant pericardial effusion is creating a pericardio-pleural shunt. As we experienced, the MCPF is just as efficient as the VATS method and it is without some disadvantages of VATS as single lung ventilation and expensive devices.
It is not advisable to perform elective pericardial fenestration based on only one echocardiography finding. The concordant finding of three imaging procedures (echo, CT and X-ray) could be the safest. Unfortunately, sometimes we have not enough time to have them before the urgent intervention. In order to avoid fatal mistakes at least two imaging procedures (echo+X-ray or CT+echo) should be necessary, especially in case of previously irradiated pericardial area.
It could be also a question whether the emergency or elective treatment of pericardial fluid is the task of general thoracic surgery. Our opinion is that the answer is definitively yes for two reasons. One of them is that heart surgery is not quickly and closely available in many regions of the country. The second reason is that the performing of pericardial fenestration can keep the surgeon in training to have the routine of working close to the heart. It is important when solving the emergency problem of a stab injury of the heart.
However, the standard and safe method for emptying pericardial fluid is the ultrasonography-guided pericardiocentesis and drainage. In case of clinical heart tamponade, in an emergency situation the best choice is the subxyphoideal fenestration. In case of pericardial effusion with malignant origin the most effective and definitive method is the creation of a pericardio-pleural shunt.

4.2.3. Conclusions

- Some changes have occured in the last decades regarding the etiology of pericardial effusions. The proportion of neoplastic origin increased. In parallel with it, the demand of oncology to apply new and effective therapeutic modalities for further definitive palliation has also increased.
- In case of mediastinoscope-controlled parasternal pericardial fenestration (MCPF) a pericardio-pleural shunt is created. It is just as effective as the VATS approach with the same good results, but without some disadvantages of VATS, such as the necessity of single lung ventilation.
- Heart surgery background is not necessary to perform pericardial fenestration. This operation is safe and keeps the thoracic surgeon in training to solve the problem of an emergency heart injury (stab wound) in a center where a heart surgeon is not accessible.

4.3. ADVANCED STAGE ESOPHAGEAL CANCER

4.3.1. Historical background

The history of esophageal surgery looks back about 300 years. The first documented esophageal operation – a collar esophagotomy - was performed in 1701 by the French surgeon *Baptiste Veduc* for removal of an impacted foreign body. The first successful animal experiment for esophageal resection was done in 1871, in Vienna, by *Theodor Billroth*. The first successful human collar esophageal resection was performed by *Czerny* (1877).
Finally, the removal of the "thankless organ" was first performed only in 1913 by an ex-German, the American surgeon *Franz J. A. Torek*. The patient had survived 13 years. Some months later *Denk* performed the first transhiatal esophageal resection without opening the thoracic cavity.
The first esophageal reconstruction (bypass) was made by *Roux* in 1907 using isolated jejunal segment.
The stomach as interposition for reconstruction was first used by *Kirschner* in 1920. *Oshawa*, in 1933, performed a distal esophageal resection (resection of the esophago-gastric junction) with intrathoracic esophago-gastrostomy. The first subtotal esophageal resection with intrathoracic anastomosis was performed in 1946 by *Ivor Lewis*.
Turner applied the first skin tube for reconstruction after transhiatal esophageal resection in 1936. The method of transhiatal esophageal resection was only renewed by *Orringer* in 1978. The lengthening of the stomach by resection of its lesser curvature and preparing a so-called "gastric-tube" was first published by *Akiyama*.
In Hungary, *Pál Rubányi* and *József Imre* engaged in pioneering activity. *Professor Imre* performed a large series of *Torek*'s operation and almost in half of them with reconstruction in a second sitting. In the field of reconstruction with a large bowel, *Zoltán Krisár* had also pioneering work in Nagyvárad.
The activity of *János Kiss* is very outstanding in the field of radical esophagectomy and he wrote some book-chapters on this theme.
The surgical school of the University of Pécs led by *Professor Örs Péter Horváth* is also outstanding. He applied microsurgical methods for free jejunal segment transplantation as reconstruction after esophageal resection for proximal cancer. He was the first in Hungary who performed a series of esophageal resections after neoadjuvant oncological treatment for locally advanced esophageal cancer.
The other big fields of the surgical treatment of esophageal cancer are stenting, endoprothesis implantation, and performing gastrostomy as palliation. The method of the Polish *Bronislaw Kader* was published in 1896. The modifications of his method are still applied nowadays for performing a gastrostomy.
The first – unsuccessful – experiment for stenting an esophageal stricture was performed by *Leroy d'Etiolles*. *Durham* introduced in 1881 an elastic orogastric feeding tube. *Krishaber* in the same year applied a nasogastric tube. *Guisez* introduced a *Pezzer*'s catheter after widening the esophageal stricture with bougie using rigid esophagoscope. The first suitable endoprosthesis was made by *Souttar* in 1924. The pull-through insertion of endoprosthesis was first used by *Mousseau* in 1956, but the first efficient pull-through type polyethylene prosthesis was introduced by *Celestin* in 1959. Many modifications of the *Souttar-Mousseau-Celestin*-like endoprosthesis were published. It was an important problem in the literature in the 1970's and 80's.
In Hungary, *Lajos Kotsis* published first his results using a self-made endoprosthesis made from a Tygon tube. Later his method was modified at the University of Debrecen by *István Kovács*.
The flexible endoscopy brought real evolution in the field of esophageal stenting. Flexible push-through type and the self-expandable stents were introduced without laparotomy (1992). In Hungary *Jenő Solt* published many papers about his experiences with different types of endoscopic esophageal stents.

4.3.2.1. Introduction

Hungary is especially affected by the problem of esophageal cancer. The incidence of esophageal cancer is salient and the age-adjusted survival of it is remarkably lower in Hungary compared with other European countries. In Hungary the situation does not seem to be improving, while in some European countries the social gradient has disappeared.
My aim was to find the medically and economically most effective surgical palliation for advanced esophageal cancer.

4.3.2.2. Materials and methods

A retrospective joint database was created from the data of the Department of General and Thoracic Surgery of Semmelweis Teaching Hospital and the data of the Department of Gastroenterology of the County Hospital, Miskolc. The joint database contained the surgical palliations between 1 January 2006 to 31 December 2010 and the endoscopic stentings between 1 September 2008 and 31 December 2011 retrospectively.
The staging of tumors happened according to the classification of the American Joint Committee on Cancer (AJCC).
In the case of locally advanced esophageal cancer the curative-palliative dichotomy is not exactly clear. Comparing the stage III-IV, R0 resected (so the theoretically curative) patients results with those of R1-2 patients, the difference in the survival is not only non-significant but nominally the latter's is better (209.6, SD: 209.9 vs. 211.8, SD: 156.85). The fact that the survival is practically the same, the low number of incomplete resected patients (n=6) and the statement that in case of esophageal cancer a direct, planned R2 resection (debulking) is not indicated led me to include the stage III-IV resections into the database for comparison between the different palliative surgical modalities. The secondary malignant strictures and the resections in stage I-II were excluded from the study. In case of tumor in the esophago-gastric junction the Siewert II-III type carcinomas were also excluded.
The patient selection for different palliative methods was decided after consultation between the thoracic surgeon and gastroenterologist. The financial background limits our possibilities in the field of endoscopic stenting. As a result the performance status of patients in the stented group was poorer than in the operative intubated group.
The type of implanted self expandable esophageal stents were Ultraflex^{TM} (Boston Scientific Co., USA) in 12 cases, Niti-S (Taewong Medical Co. Ltd., Korea) in 4 cases, Wallflex (Boston Scientific Co., USA) and Clearview (PAN Medical Co., UK) in 1-1 cases.
Resection was decided when - according to the data of examinations - the tumor seemed to be resectable and distant metastasis was not known. Usually a gastric tube according to Akiyama was used for the replacement of the resected esophagus. The gastro-esophageal anastomosis was intrathoracic or collar depending on the position of the tumor (middle or distal third), and the length and the quality of blood supply of the gastric tube. The type of the anastomosis was telescopic or single-layer continuous with double-needle technique. Our main principle was that a shorter resection with non-stretched anastomosis is much better for palliation than leakage or interpositum necrosis after an extended resection. In case of irresecability, pull-through esophageal intubation was applied (n=8). A gastrostomy was performed according to Kader in case of unsuccessful pull-through intubation or endoscopic stenting.

4.3.2.3. Our self-made tube and the technique of operative intubation

The procedure was performed in all cases using a self-made Souttar-Mousseau-Celestin-like Kovács-Kotsis kind of prosthesis prepared from plastic Tygon tube (Tygon® Medical/Surgical Tubing 1/2" ID X 3/4" OD X 1/8" Wall). The length of the tube was between 10 and 20 cm.
In general anesthesia an esophagoscopy was performed using a rigid esophagoscope, and the tumorous stenosis was widened with an increasing diameter bougie set. At the diameter of 16-18 Ch (1 Charierre = 0,33 mm) a pulling catheter was fixed to the end of the bougie and pushed out from the stomach through a small gastrotomy taken in the mid-anterior surface. The Tygon tube was pulled through the tumor with the help of this catheter. When necessary, we applied a combined push-pull method.

4.3.2.4. Results

There were 209 operations and 35 endoscopic stentings, altogether 244 interventions for esophageal malignancy in our database in the examined period. Patients lower than stage III cancer, or having not primary esophageal malignancy were excluded. This way, 145 palliative operations and 18 endoscopic stentings, altogether 163 patients underwent some kind of invasive or operative palliation in the examined period for primary esophageal cancer. The demographic data and the anamnestic and clinical features of patients (the duration of dysphagia, the rate of smokers and heavy drinkers, the localization of tumor, the palliation procedures) and the histology are shown in *Table II.* and *Table III.*
We had altogether 14 patients (8.58%), who were non-smokers; alcoholism was not explored and they had not considerable disease in their anamnesis (ASA1-2).
The mean age of resected patients was lower than the other groups. This can indicate that we decided to perform resection in younger patients. The mean age in the endoprothesis and self-expandable stent group was the highest. The mean age of the gastrostomy group was between the resected and stented group.
More than half of patients lost more than 11 kg before the first medical examination. More than half of patients stated more than 2 months dysphagia before first consulting a physician.
In 52 cases of stage III-IV patients we decided to perform resection and 43 of them were resectable (83%). In 8 cases of the 9 irresectable patients, pull-through esophageal intubation could be performed at the same sitting. In one case, it was only possible to perform gastrostomy. The rate of postoperative complications was the highest in case of resection. The total postoperative mortality was 7% (3/43).

Table II.: Demography data (with censored cases)

	Valid N of patients	Mean age	Min.	Max.	Standard Deviation	%
Male	139/163	59.8666	29	89	10.1467	85.27%
Female	24/163	61.4511	49	84	8.5030	14.72%
Altogether	**163/163**	**60.5369**	**29**	**89**	**9.9746**	**100%**
Resection	43/163	57.5581	29	74	8.9557	26.38%
Endoprothesis	62/163	65.3709	42	84	9.2030	38.03%
Gastrostomy	40/163	60.9000	41	84	10.53882	24.53%
Stent	18/163	64.1666	50	89	9.5993	11.04%
Patients with oncological care						
Resection	22/43	58.1818	29	74	9.7815	51.16%
Endoprothesis	31/62	62.6129	42	76	6.5047	50.00%
Gastrostomy	26/40	58.9230	45	77	8.3470	65.00%
Stent	16/18	62.8125	50	75	7.7907	88.88%
Altogether	95/163	60.6105	29	77	8.2104	**58.28%**
Negative anamnesis, non-smoker, non-drinker						
Altogether	14/163	65.2143	42	80	11.9175	**8.58%**

Table III.: Duration of dysphagia, weight loss, harmful habits, histology and localization of tumor (with censored cases)

	Valid N of patients	Mean	Min.	Max.	Standard Deviation	%
Dur. of dysphagia	147	3.6598 months	1 month	30 months	3.8436	
Weight loss	61	11.21 kg	0 kg	35 kg	6.5450	
1.Smokers	106/163					66.66%
2.Drinkers	82/163					51.57%
1. and/or 2.	124/163					77.98%
Histology						
Adenocarcinoma	29/163					17,79%
Squamous-cell cc.	134/163					82.21%
Localisation						
Proximal third	19/163					11.66%
Middle third	77/163					47.24%
Distal third	67/163					41.10%

Pull-through esophageal endoprothesis implantation was indicated in 75 cases. The success rate was 83% (62/75). In the unsuccessful 13 cases gastrostomy was performed at the same sitting. As postoperative complication a displacement of the implanted endoprothesis happened in 5/62 cases (8%).
The success rate of self-expandable endoscopic esophageal stentings was 94% (17/18) and there was no stent migration.
There were 4 complications in the gastrostomy group: all the four cases were wound-healing abnormalities.
The cumulative survival of our all esophageal cancer patients was 138 days. This data is considered a basic number. The survival of our resected patients is salient. Within this group the survival of patients with oncological treatment is higher. The survival of the 14 low-risk patients was also above the basic number (221 vs. 138 days, 160%) independent of the type of intervention (5 resections, 5 endoprothesis, 3 self-expandable stents and 1 gastrostomy).
Comparing the survivals of the four groups only, the survival of resected patients differs significantly from the other three groups. There is no significant difference regarding survival between the non-resected groups.
The oncological care was advantageous regarding survival only in the resected group. The presence of co-morbidities involving one or more organs decreases the survival chance.

4.3.2.5. Discussion

Advanced esophageal cancer causes both physical and spiritual complaints in consequence of dysphagia and malnutrition. The ideal surgical palliation should solve both problems. All of the invasive or surgical interventions for advanced esophageal cancer have advantages and disadvantages. Furthermore, *the choice from the different methods is not a free medical decision. It is made possible or must be rejected by some circumstances.*
Unfortunately, the definition of "palliative esophageal resection" is not clarified in the literature. Usually the incomplete (R1, R2) resection is reckoned as palliative. Others say that the resection with positive lymph nodes is also palliative. Anyway, the palliative esophageal resection is not a goal in

itself but a result. The risk of surgery is salient and the complications can be fatal. The tumor mass reduction, the planned R1 or R2 debulking type of resection is not indicated in case of esophageal cancer. The anastomosis itself is also a risk factor. In our study the resection provides the chance of longest survival with the best quality of life.
The resection has the highest postoperative mortality risk in our material, similarly to the data of the literature.
The patient who is ideally suitable for surgical palliation would be locally resectable, without distant metastasis, well nourished, having not harmful habits and has got neoadjuvant oncological treatment with good response. We had no such patient in our database.
The pull-through esophageal intubation is an old, well-known method with numerous versions and modifications. The reason why we developed our self-made tube was simply economics. We have used it for more than 30 years. We think it just as effective as any industrial set. The disadvantage of the pull-through method is the general disadvantage or chance of complications involved in laparotomy and gastrotomy. The risk of implant migration is relatively high, varying up to 14%, (in our own material 8%) and the replacement can usually be performed with reoperation. In case of upper third esophageal cancer, it is frequently not possible to perform pull-through intubation. At least a 3-4 cm long free section of the esophagus is needed to start the swallowing process.
The self-expandable endoscopic esophageal stenting would be the ideal palliation in case of locally advanced esophageal cancer. It has all of the advantages of esophageal intubation without the general risks of surgical operations. Nowadays, this method should be the first choice. Unfortunately, the economic conditions determine our own possibilities.
The gastrostomy must be the last choice, the "ultimum refugium". This method has no advantage compared with other methods. It is especially disadvantageous regarding the quality of life.
The perioperative oncological treatment improved the survival in our palliative resected patients, but it had no influence in cases of patients who underwent other types of palliation. On the other hand complications increase after stenting with prior radio-chemotherapy. But radiotherapy after stenting can improve the stent's patency.

4.3.3. Conclusions

The conclusions of this retrospective study are limited, because:

- the notion of palliative resection in case of advanced esophageal cancer is uncertain. The outcome of the resection and the disease-process indicates the effect of the intervention. We performed a low number of R1, R2 resections in this group which were unsuitable for comparison and statistical analysis.
- the indication of application of self-expandable stents was determined by extramedical, extraprofessional principles.
- the chances of operative intubated patients (pull-through endoprothesis and gastrostomy) were originally better than those in the stented group. This advantage was kept even postoperatively. So their results were better, although not significantly.

The most effective and the simplest method is introducing a self-expandable stent; consequently, this method is preferred all over the world. Our self-made pull-through type device is also simple and cheaper than that if we do not calculate:

- the operative time (41700 HUF/hour – without material cost and amortization)
- the cost of narcosis (21960 HUF/hour – without material cost and amortization)
- giving the patient pain by a laparotomy
- the length of hospital stay (18312 HUF/day/bed – without material cost, amortization. Source: Department of Finance of the hospital)

So, the current situation does not support the modern intervention.

We can verify, based on the retrospective study that:

- the oncological treatment was advantageous concerning survival in case of resected advanced stage esophageal cancer patients.
- on the other hand, the oncological treatment was not advantageous (neutral) in cases of non-resected patients.
- the survival of low-risk patients without harmful habits was significantly longer. The reserves of a slightly worn-out organ provided extra months.
- the co-morbidities decreased the survival most of all in the resected patients' group.

5. FINAL CONCLUSIONS

1) According to the objectives, I have summed up the historical background of the examined methods. The first myocardial suture can not be reckoned as the first cardiac surgery intervention, but it was the first pericardium fenestration. In contrast with the public belief the first documented pericardium fenestration was performed by the Spanish Francisco Romero and not the French Baron Dominique Jean Larrey, as I have published in international forum.
2) The role of thoracic surgical diagnostic and palliative intervention is continually increasing as part of the complex treatment of upper mediastinal masses. The reason for this is the demand for more and better quality tissue for the pathological decisions needed for the increasingly effective oncological, biological (target) therapy. The morbiditiy and mortality rate of minimally invasive surgical methods decreased; however, the attainable information content of tissue samplings obtained from endoscopic examination is much behind that of the operative specimen. I have proved based on the results of a significant national material, that the importance of surgery – in contrast to the decreasing rule in other areas – and the collar and parasternal mediastinoscopy in the upper mediastinum is still constant. In certain cases of rare mediastinal tumors – due to the lack of other effective therapeutic modalities – the extended resection is applicable.
3) I have proved that general thoracic surgical experience is enough for performing palliative interventions on the pericardium – a heart surgical background is not needed. I have disclosed that this type of operation keeps even the general surgeon with thoracic surgical background in training to maintain the essential expertise to perform those emergency heart operations (penetrative wounds) which are otherwise in the curriculum.
4) The definitive elimination of malignant pericardial effusions without recurrence makes possible further oncological treatment. The mediastinoscope-controlled parasternal pericardial fenestration we have developed seems to be a good method as it is proved by its national and international acceptance. This approach is simple, cheap, easy and quickly performed, and easy to tolerate by the patient. It has the same effectiveness as the other known and accepted methods.
5) The surgical palliation of advanced esophageal cancer is made difficult by the polymorbidity and bad socio-economic status of patients. I have demonstrated that the cooperation between the surgeon and oncologist resulted in the best survival chance. I have proved that the resection as part of multimodal treatment was the most promising solution. Our self-made pull-through esophageal endoprothesis has no disadvantages in the Hungarian health care compared with the industrial sets. The device itself is cheap; the method is easy to learn and perform. In spite of this fact, it is hardly the ultimate ideal solution. The proportion of application of self-expandable esophageal stents should be improved in the case of palliation of the advanced irresectable esophageal cancer.