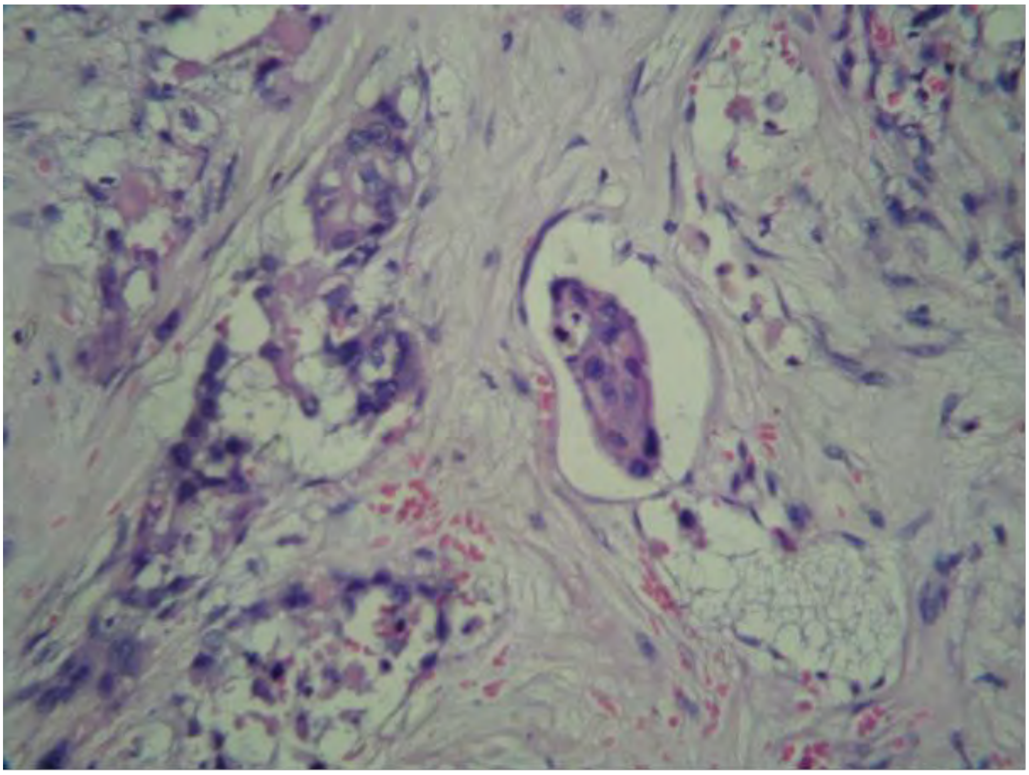
MEDICAL UNIVERSITY - town of PLOVDIV

FACULTY OF MEDICINE

DEPARTMENT OF “SPECIALIZED SURGERY”

Dr. Yordan Toshev Tsenovski

THE ROLE OF LYMPHATIC VASCULAR INVASION IN THE PROGNOSIS OF OESOPHAGEAL CARCINOMA



ABSTRACT

of dissertation thesis for awarding an educational and scientific degree

“DOCTOR OF SCIENCES”

Scientific specialty "Thoracic Surgery” 03.01.44

Scientific supervisor:

Dr. Georgi Tsvetkov Prisadov, Assoc. Prof., MD

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The patients included in the study, carried out for the dissertation, were operated in First surgical clinic of "Pirogov" Hospital, Sofia. Pathohistological examinations were performed in the Department of Pathological Anatomy of "Pirogov" Hospital , Sofia.

The dissertation contains 195 pages with 14 appendices and is illustrated with 23 photos, 55 figures and 7 tables. The bibliography includes 178 authors, of which 5 in Cyrillic and 173 in Latin.

The dissertation thesis is approved and admitted for official defence by an extended department council of the Department of Special Surgery, Medical University - Plovdiv.

The public defence of the dissertation will take place at …………… from …… o'clock in ……… auditorium of MU Plovdiv, Blvd. "Vasil Aprilov" 15A at an open meeting of the scientific jury composed of:

Internal members:

1 Prof. Dr. Angel Petrov Uchikov, MD

2 Prof. Dr. Rosen Stoyanov Dimov, MD

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The dissertation materials are available in the Library of the Medical University - Plovdiv.

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ABBREVIATIONS USED

In Cyrillic

GEP - gastroesophagoplasty

IHC - immunohistochemistry

LN - Lymph Nodes

LVI - Lymphovascular Invasion

LSTTTDA - Left-Sided Transthoracic Transdiaphragmatic Access

p63 - Protein 63

CK7 Cytokeratin 7

H&E - Hematoxylin and Eosin

In Latin

ITC - Isolated tumour cells

LNR - Lymph Node Ratio

SM - Skip Metastases

3FLD - 3-Field Lymphadenectomy

2FLD - 2-Field Lymphadenectomy

1. INTRODUCTION

Modern oncological diagnosis has an integrative character. Its purpose is to integrate the accurate diagnosis, determined by diagnostic imaging techniques and obligatorily by pathomorphological verification, as they justify the prognostic and predictive factors. The latter are determined by the histological type of the tumour and the extent of its spread. Those principles underlie the TNM tumour staging system, accepted by WHO, and include the size and spread of the tumour in the primary organ, the lymphatic status, the presence or absence of metastases and conditions of resection lines. In some tumours of the gastrointestinal tract with TNM staging is necessary to further determine lymphatic vascular embolization and perineural infiltration. In oesophageal carcinoma, vascular invasion is not included in TNM staging. Literature data indicate that this invasion is an independent prognostic factor in cases of squamous cell carcinoma of the oesophagus and adenocarcinoma of the stomach. The question of its role in distal oesophageal adenocarcinoma and oesophago-gastric junction is still under discussion. Of particular interest in this regard is to clarify the role of the vascular invasion, which precedes lymphogenic metastases. In the light of the submitted data, it is important to examine what proportion of oesophageal and oesophago-gastric junctions carcinomas show embolization in lymphatic and venous vessels in the N0 phase of tumours, when no lymphogenic metastases have been detected. Clarifying this issue can help us to determine how to conduct the adjuvant therapy. The results confirm that there is a difference between oesophageal adenocarcinoma and squamous cell carcinoma concerning the tumour biology, etiology and pathogenesis. Here the problem of specifying the prognostic factors is particularly important, especially since some significant prognostic and predictive features are not clarified. One of these features is the lymphatic vascular invasion (LVI). LVI is an important component of tumour progression and is defined as an independent prognostic factor for many tumours. Based on the assumption that the inclusion of LVI is an essential sign, showing the onset of aggressive carcinoma behaviour, it is important to study the role of LVI in the progression of oesophageal and oesophago-gastric junction carcinomas in different stages of tumours, in different histological types and compare its presence with lymphogenic metastases. The accurate determination of the lymphovascular invasion in the GI tract tumours and especially in cases of oesophageal carcinoma, has its place in the modern oncological diagnosis. Along with the diagnosis of the tumour type, it is necessary to specify the prognostic and predictive factors. They largely depend on the stage of the tumour spread and respectively on the vascular invasion and the regional lymph node involvement. It is important to know is there invasion in the lymph vessels before it has appeared in the lymph nodes and possibly in what percentage of cases. Based upon the assumption of the different ways the tumour progresses, we support the view that in all cases of carcinomas of the distal oesophagus, a systematic study of tumour neovascularization and reporting of LVI are necessary. Given the difficulties that may arise in the detection of tumour embolism, IHC tests with Cytokeratins are performed to distinguish objectively tumour cells from blood cells. It is well known that the transmission of tumour embolism happens through the activation of the coagulation factors and the adhesion of blood elements in the circulation. With such a premise, tumour cells can change their typical characteristics, or to manifest them only with single cells, so that IHC test is an indispensable tool. Lymphatic invasion is considered an independent prognostic factor. This invasion precedes or occurs simultaneously with lymph node metastases. Nevertheless, in patients with early carcinoma (T1) and carcinoma without the involvement of nodular metastases (N0), lymph vessel invasion is often detected. This is due to the aggressiveness of these tumours.

The staging is strictly defined by the TNM system adopted by the WHO and published by the AJCC / American Joint Committee of Cancer / and UICC / Union for International Cancer Control/. A number of authors note that the last eighth classification of the TNM system of AJCC and UICC from 2017 is not satisfactory and complete, as it does not take into account all the factors characterizing oesophageal cancer. The search for the creation of a more complete and optimized system for evaluation of oesophageal carcinoma continues. Efforts are currently being made to improve staging methods. Undoubtedly, the characteristic lymph flow underlies the specific features in which the oesophageal carcinoma spreads. The determination of lymphatic vascular invasion (LVI) in GIT tumours is increasingly used as a postoperative prognostic factor. Lymphatic dissection volume is included in these additional methods for assessing and staging this most aggressive visceral carcinoma. Modern multimodal therapy requires even greater precision in the classification and staging of the disease in each individual patient and the introduction of a unified system. The detailed classification allows for targeted dissection of a larger number of lymph nodes by groups, improving staging and oncological radicalism. Despite the success of surgical and combination treatment of oesophageal carcinoma, the overall 5-year survival currently remains below 10%. Oesophageal cancer is a common tumour with a tendency to increase its frequency, characterized by high resistance to modern methods of treatment and high mortality.

2. CLINICAL STUDY

2.1. OBJECTIVES AND TASKS

2.1.1. OBJECTIVES

1. INVESTIGATE THE ROLE OF LVI IN THE PROGRESSION OF THE TWO MAIN TYPES OF OESOPHAGEAL CARCINOMA AND OESOPHAGO-GASTRIC JUNCTION IN THE DIFFERENT STAGES OF TUMOUR AND COMPARE THEM WITH LYMPHOGENIC METASTASIS.

2. EVALUATE THE OPPORTUNITY FOR LYMPH DISSECTION ACCORDING TO THE TYPE OF SURGICAL INTERVENTION

2.1.2. TASKS

1. INVESTIGATE HOW MUCH CARCINOMAS OF THE OESOPHAGUS AND CARDIA SHOW TUMOUR EMBOLIZATION IN THE LYMPH AND VENOUS VESSELS IN PHASE N0.

2. DETERMINE THE TUMOUR EMBOLISATION IN TUMOURS IN STAGE N 1, WHEN NO SKIP METAPASES ARE PROVEN.

3. BASED ON THESE DATA DETERMINE THE INDICATIONS FOR CONDUCTING NON-ADJUVANT AND ADJUSTANT THERAPY.

3. MATERIAL AND METHODS

3.1. MATERIALS

CLINICAL CONTINGENT

- AMBISPECTIVE ANALYSIS OF PATIENTS OPERATED THE LAST 6 YEARS IN FIRST SURGICAL CLINIC OF “PIROGOV” HOSPITAL - SOFIA.

2 YEARS RETROSPECTIVE ANALYSIS BY DOCUMENTS - 2010 - 2011

4 YEARS PROSPECTIVE ANALYSIS BY DOCUMENTS - 2012 - 2016

We have operated on 188 patients. The method we choose is lymph dissection in 2 areas. Depending on the location of the tumour, established by the paraclinical examinations and the preoperative staging, we perform a radical surgical intervention with a lymph dissection trough an appropriate access. The resectate is examined on an intraoperative frozen section and after that, a permanent histological fixation.

3.2. METHODS

Fifty cases of tumours of the distal oesophagus and gastroesophageal ligament were studied, distributed according to their location and histological type of adenocarcinoma or squamous cell carcinoma. In 18 cases, the tumours are in stage N0 and in 32 - in stage N1. Histological methods were applied - routine histological examination with Hematoxylin and eosin stain, Pas reaction and immunohistochemical examination if necessary. Immunohistochemical analysis were performed on formalin-fixed and paraffin-embedded blocks. The sections were treated according to the method proposed by DAKO and antibodies against p63, SK-7, SK poly and SD-34 were used. /Photos 1, 2, 3, 4, 5, 6, 7/

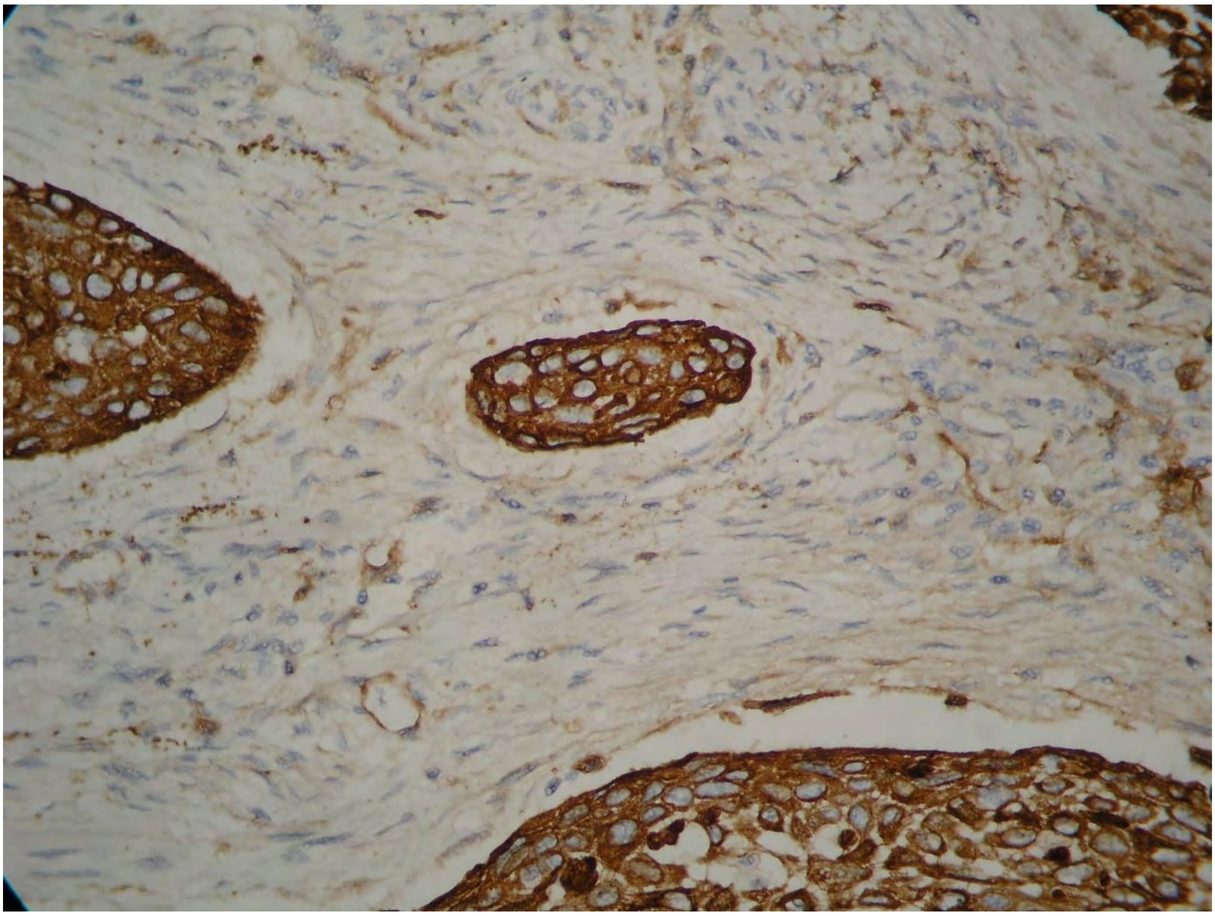


Photo 1. Massive embolization of adenocarcinoma IHC for Cytokeratin 7.

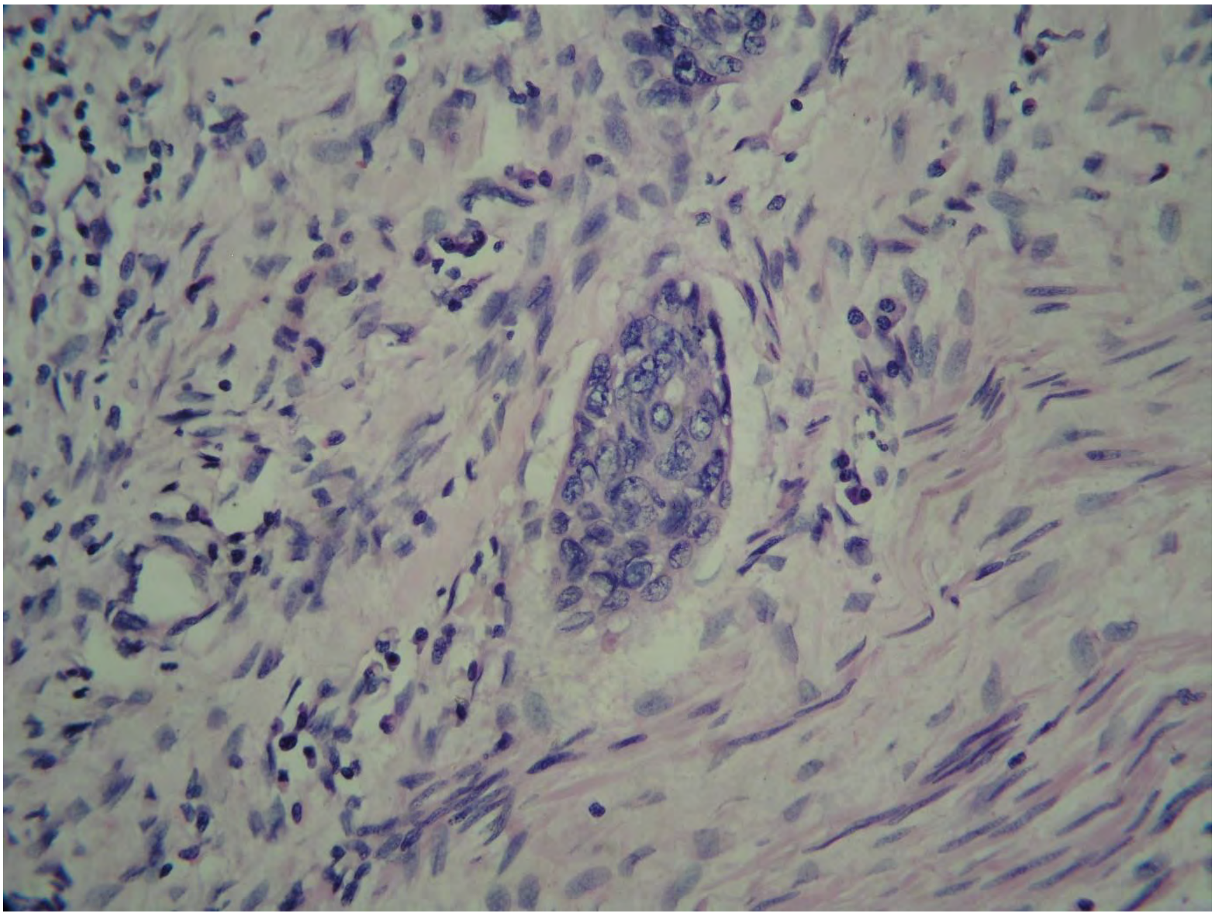


Photo 2. Lymph vessel tumour embolism in the infiltrative zone of adenocarcinoma. Colouring H&E stain

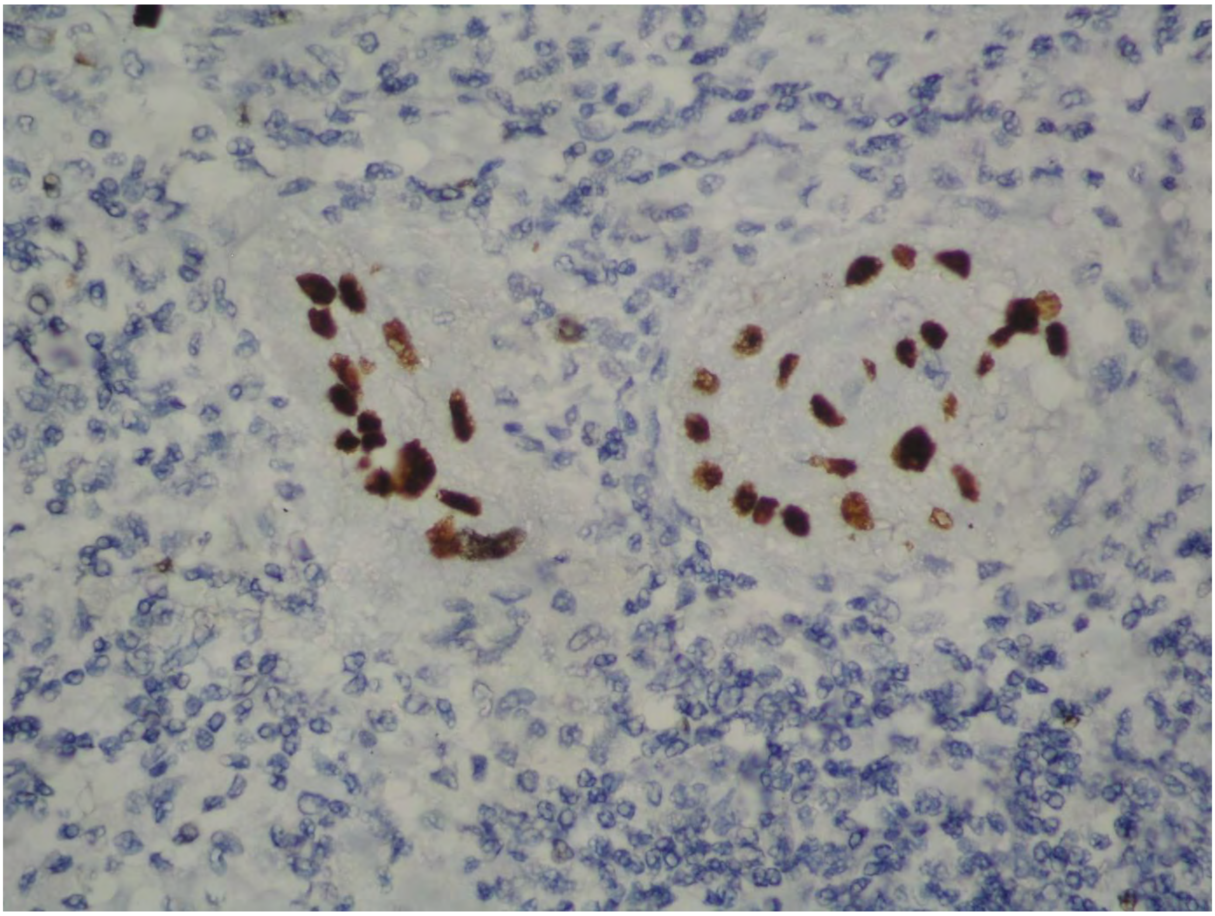


Photo 3. LVI from moderately differentiated oesophageal squamous cell carcinoma IHC with p63

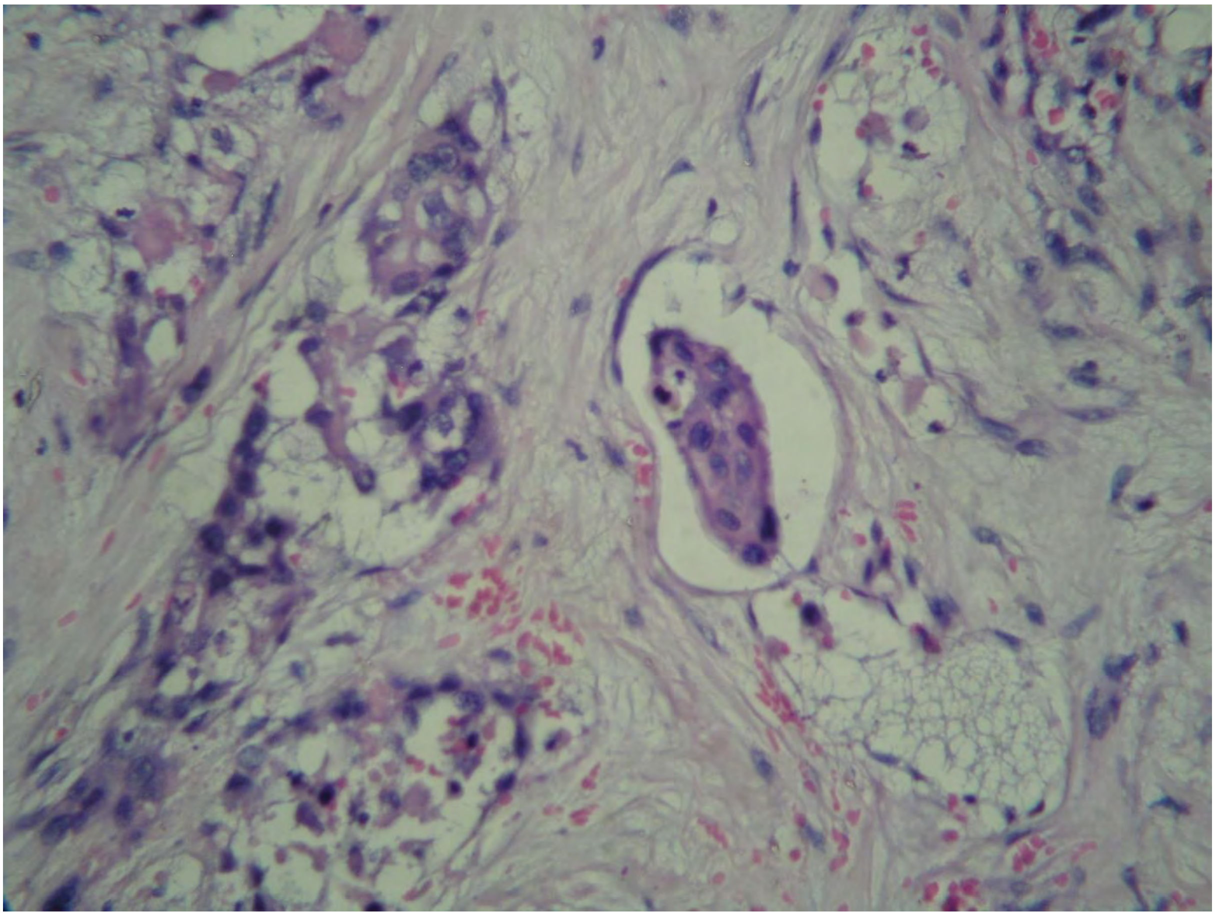


Photo 4. Invasive area of adenocarcinoma with tumour embolism in lymphatic vessel. H&E stain

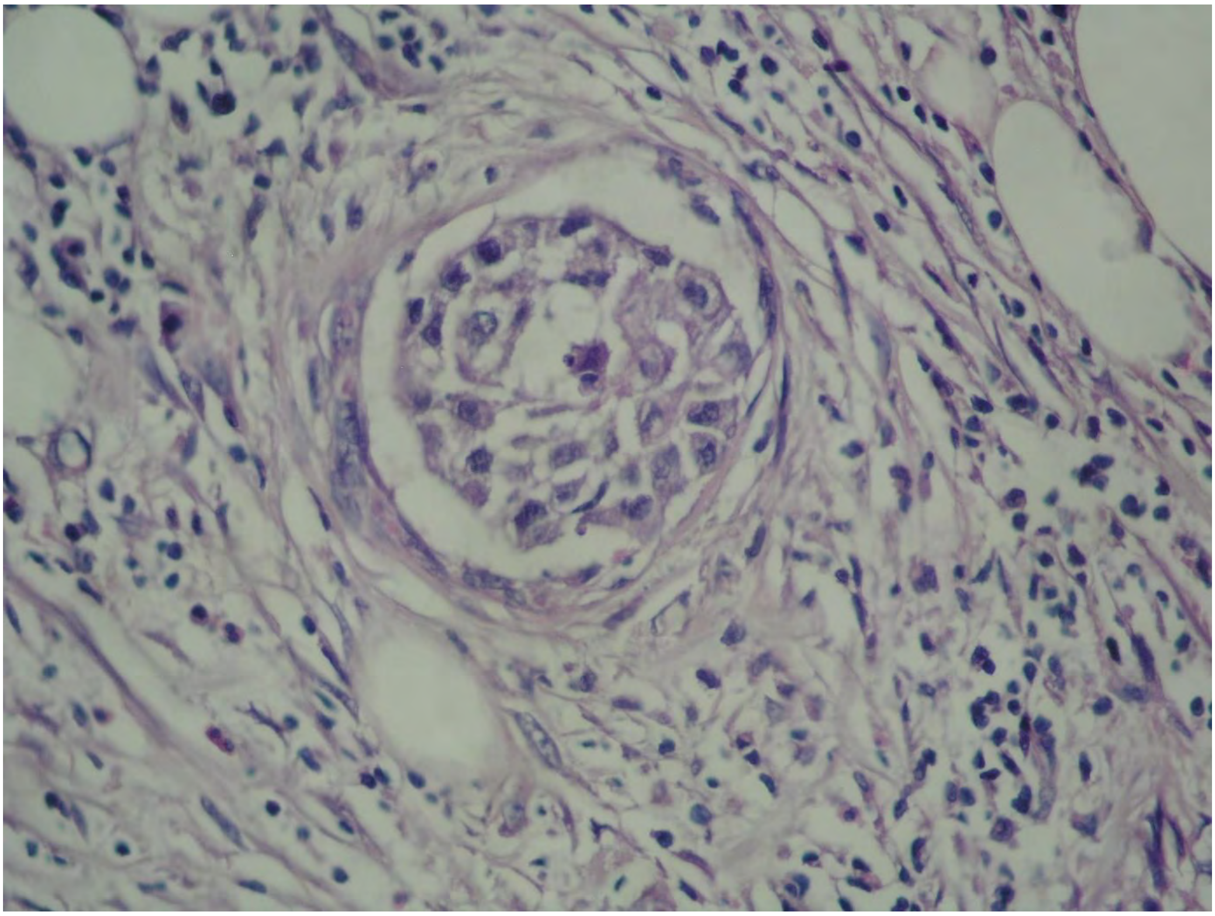


Photo 5. Tumour embolism of squamous cell carcinoma in perigastric tissue in stage N0. Colouring H&E stain

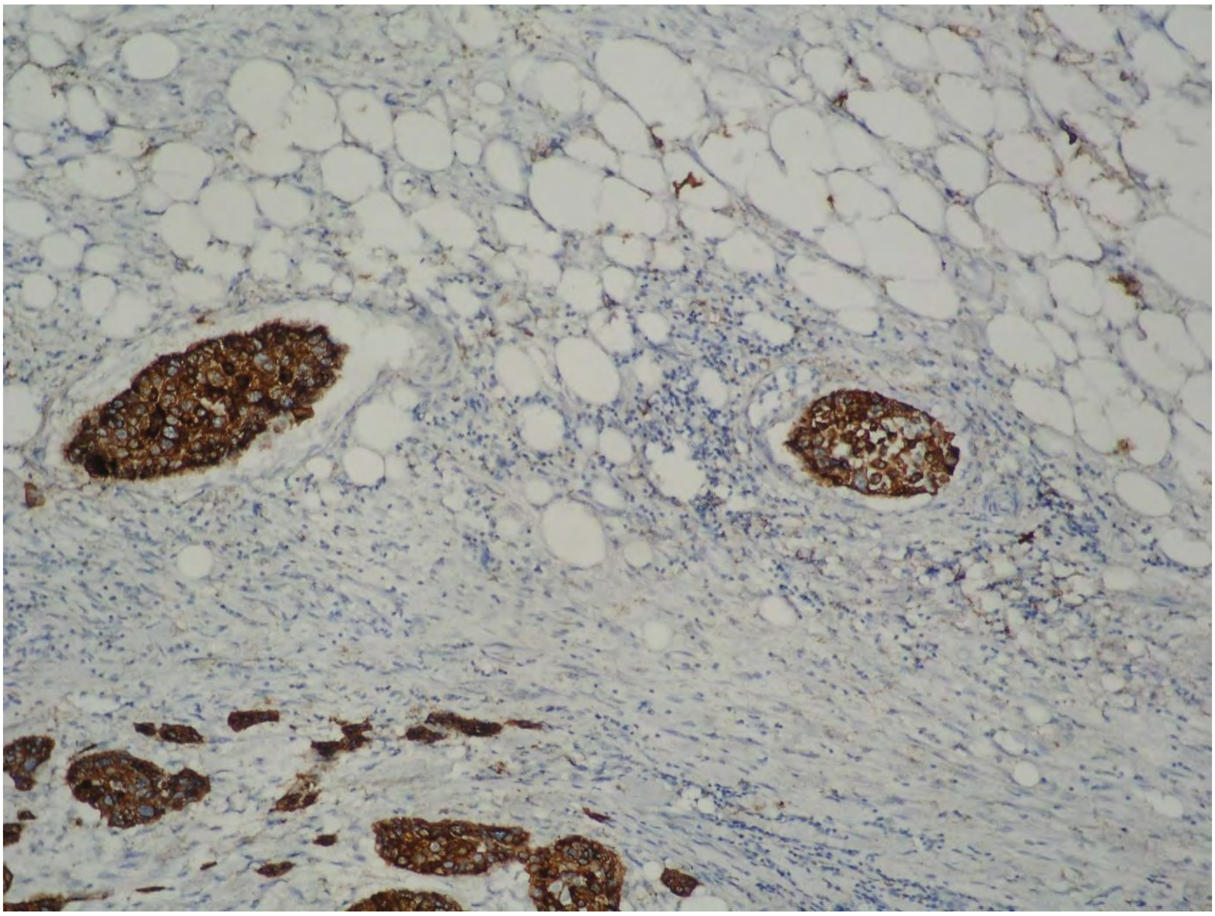


Photo 6. LVI from moderately differentiated adenocarcinoma of the gastroesophageal ligament in perigastric tissue with reactive inflammation. IHC for CK7.

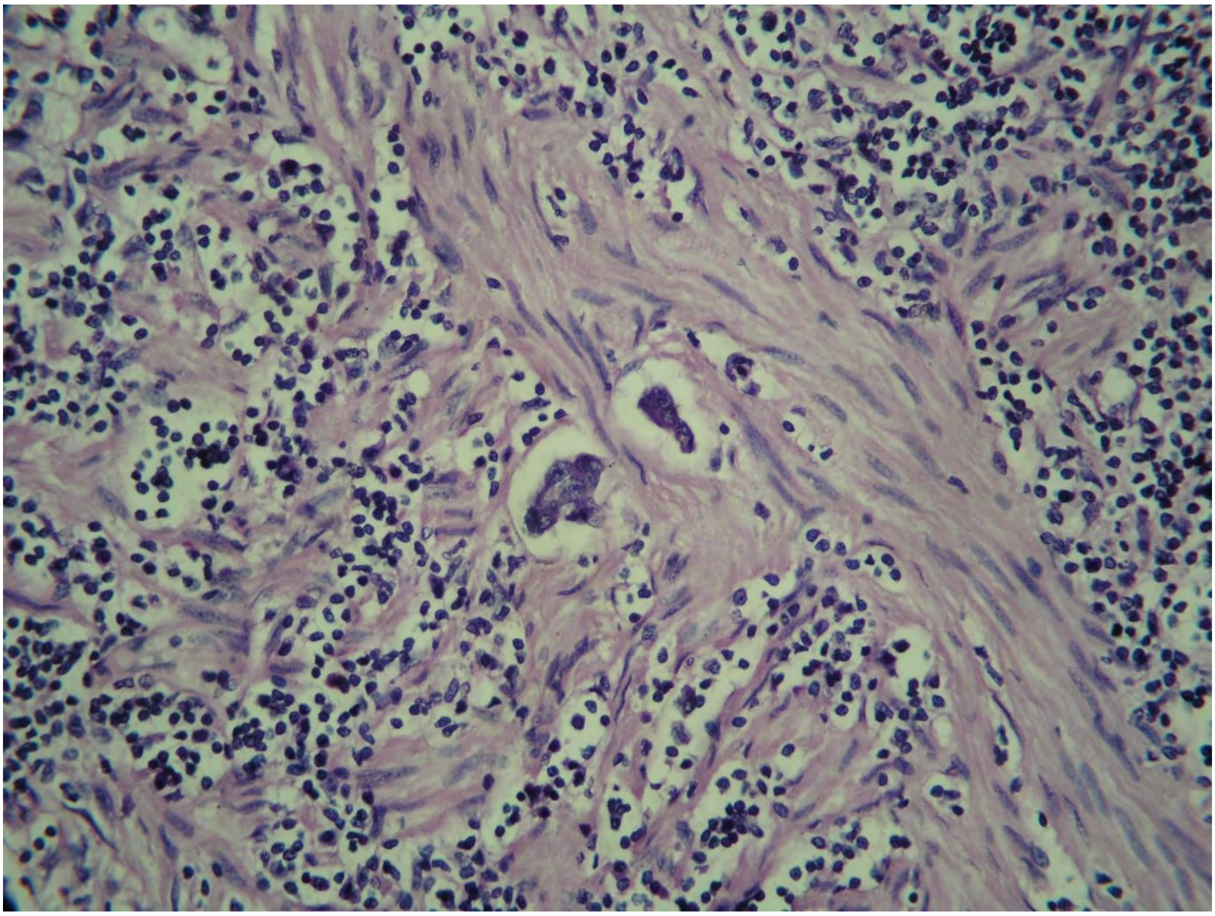


Photo 7. Early lymph node LVI without true metastasis of poorly differentiated gastroesophageal adenocarcinoma. Colouring H&E stain

4. RESULTS AND DISCUSSION

LVI in adenocarcinoma with lymphogenic metastases (N1-N3): a total of 18 cases, of which 5 cases studied with IHC - all with LVI (100%).

LVI in adenocarcinoma with lymphogenic metastases (N0): a total of 9 cases, of which 4 cases studied with IHC - in 3 of them LVI was found (75%).

In Stage I - 2

In Stage II - 5

In Stage III - 0

In Stage IV - 2

LVI in squamous cell carcinoma with lymphogenic metastases (N1-N3): a total of 14 cases of which 5 cases studied with IHC - all with LVI (100%).

LVI in squamous cell carcinoma with lymphogenic metastases (N0): a total of 9 cases, of which 4 cases studied with IHC - in 3 of them LVI was found (75%).

In Stage II - 2

In Stage II - 6

In Stages III - 1

In Stage IV - 0

In the study with IHC /immunohistochemistry/ methods in 8 of 18 cases (44%) without lymphogenic metastases and in 6 of them (75%) we found LVI. Of these 6 cases, 3 were with adenocarcinoma and 3 were with squamous cell carcinoma; in only 2 of them LVI could be assessed with H&E stain and in the remaining 4, IHC studies were crucial.

- IN ALL CASES WITH LYMPHOGENIC METASTASIS WE HAVE ESTABLISHED THE PRESENCE OF INVASION IN LYMPH VESSELS.

- HOWEVER, THE INTENSITY OF EMBOLIZATION DOES NOT ALWAYS CORRESPOND TO THE SIZE AND NUMBER OF METASTATIC LYMPH NODES.

- THE DETECTION OF TUMOR EMBOLIESM INCREASES CARRYING OUT SERIAL TESTING IN PERITUMOR AND PERINODAL TISSUE.

1. By gender - For a 6-year period 188 patients were operated, of which men - 151 and women - 37. The percentage ratio is men - 80% and women - 20%. /Fig. 1/

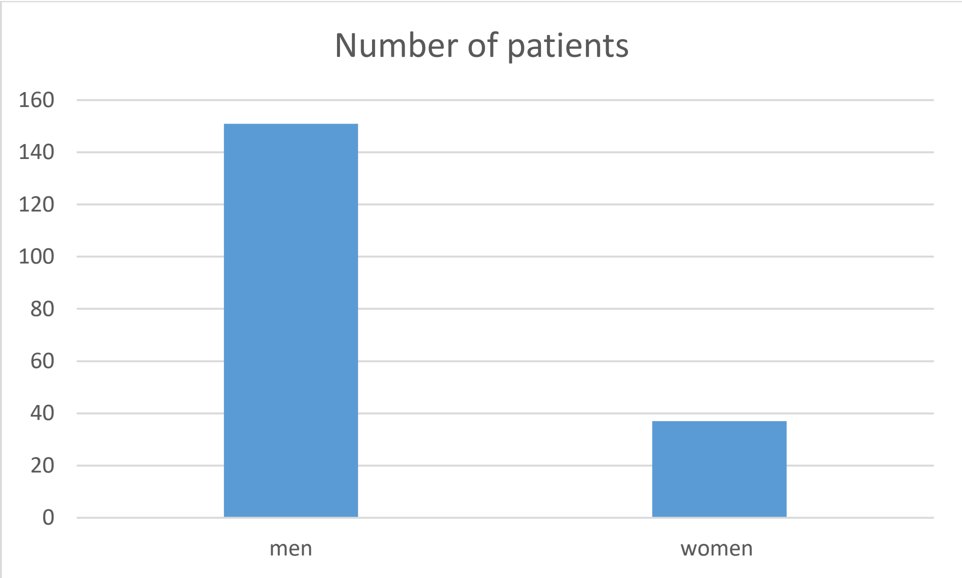


Fig. 1 - Number of patients by sex

2. By decades	**20-30 year-old-1**	**0,5%**	
	30-40 year-old-6	**3,1%**	
	40-50 year-old-27	**14,6%**	
	50-60 year-old-61	**32,4%**	
	60-70 year-old-66	**35,1%**	
	70-80 year-old-26	**13,8%**	
	80-90 year-old-1	**0,5%**	**/Fig. 2/**

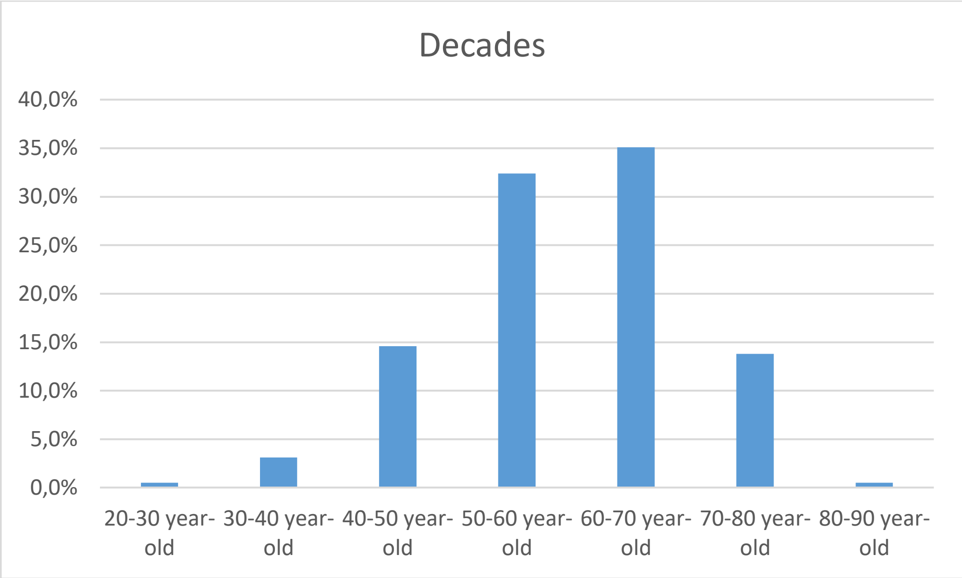


Fig. 2 - Patients by decades

3. Men by decades	**20-30 year-old-1**	**0,7%**
	30-40 year-old-5	**3,3%**
	40- 50 year-old-23	**15,2%**
	50- 60 year-old-51	**33,8%**
	60-70 year-old-49	**32,5%**
	70-80 year-old-22	**14,5%**
	80-90 year-old -	**0%**

/Fig. 3/

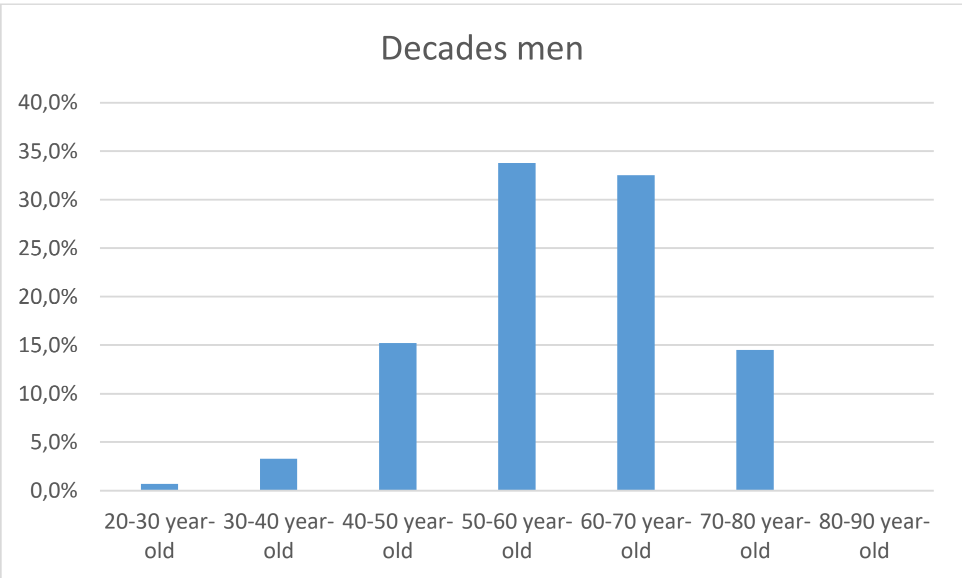


Fig. 3 - Men by decades

Women by decades	**20-30 year-old –**	**0%**
	30-40 year-old-1	**2,7%**
	40- 50 year-old-4	**10,8%**
	50- 60 year-old-10	**27,1%**
	60-70 year-old-17	**45,9%**
	70-80 year-old-4	**10,8%**
	80-80 year-old-1	**2,7% /Fig. 4/**

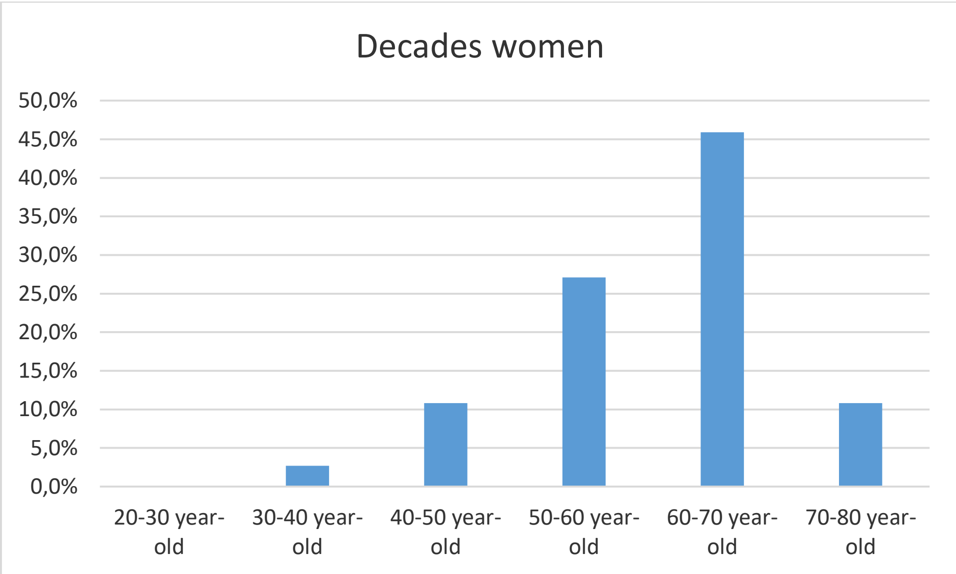


Fig. 4 - Women by decades

4. By localization	**Siebert 1-**	**60**	**32%**	
	Siebert 2-	**26**	**14%**	
	Siebert 3-	**38**	**20%**	
	Distal third-	**25**	**13%**	
	Middle third-	**33**	**18%**	
	Cervical-	**6**	**3%**	**/Fig. 5/**

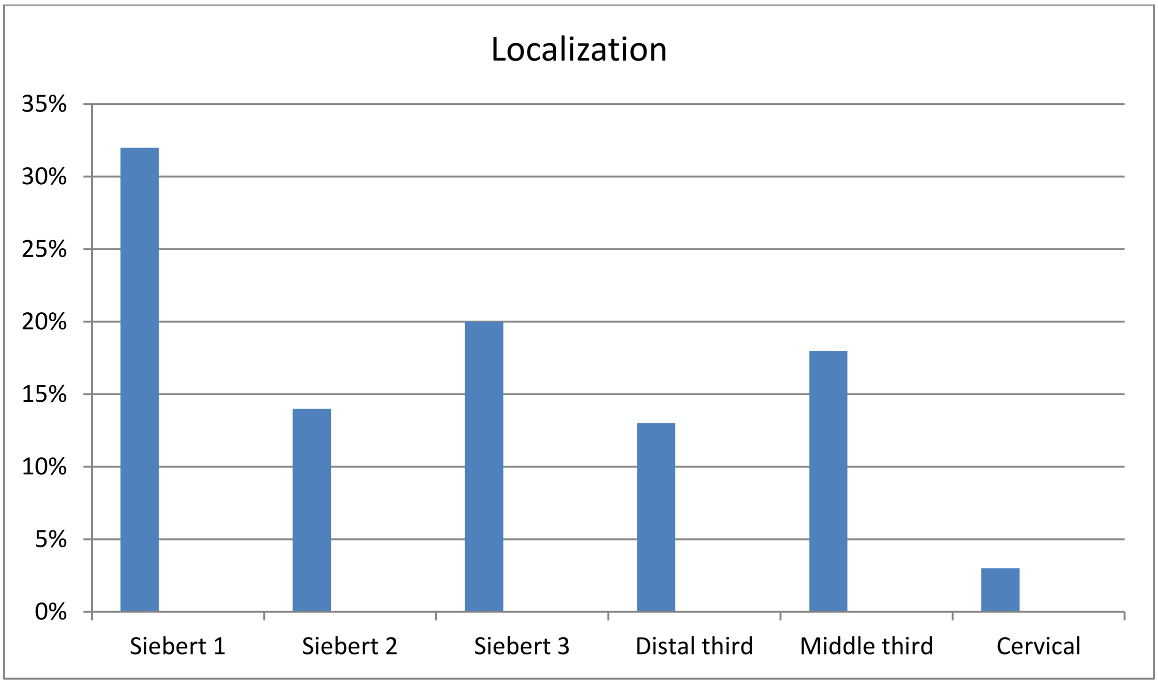


Fig. 5 – By localization

5. Access	**Laparotomy + Right thoracotomy -**	**17**	**9%**	
	Left Thoracophrenotomy –	**129**	**69%**	
	Laparotomy + Cervicotomy –	**17**	**9%**	
	Combined / VATS + L-scopy/ –	**25**	**13%**	**/Fig. 6/**

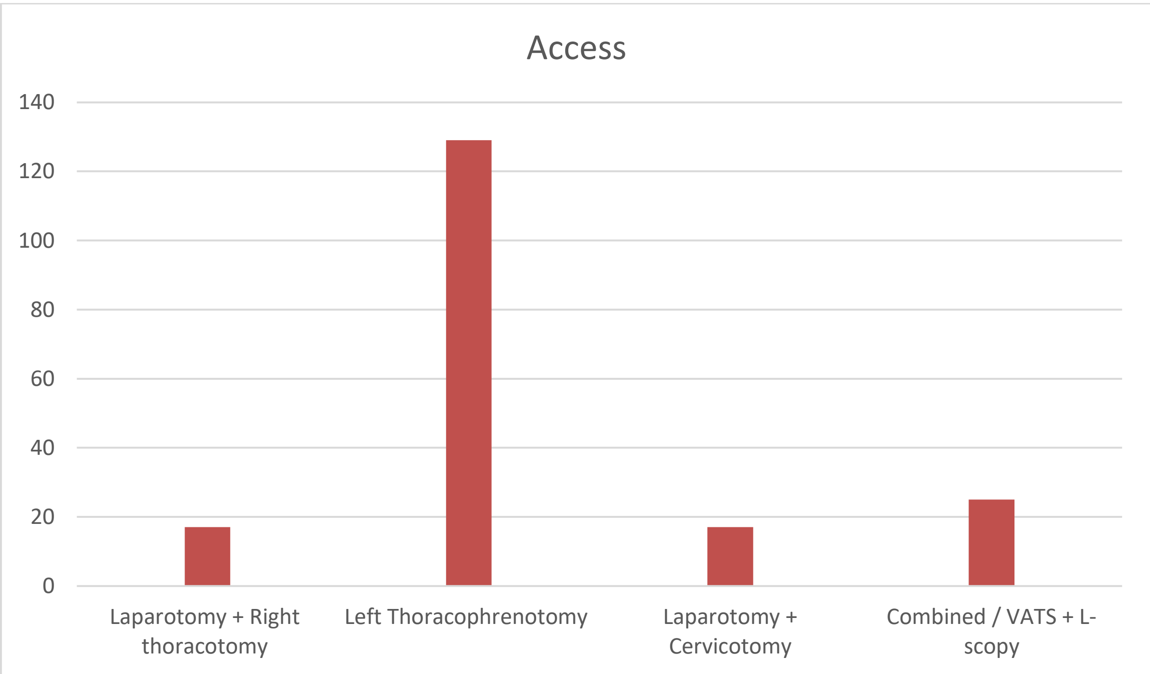


Fig. 6 - Accesses

6. Blood loss	**Minimum <300 ml. –**	**162**	**86%**
	Moderate 300-600 ml. –	**18**	**10%**
	Significant> 600 ml. –	**8**	**4%**

/Fig. 7/

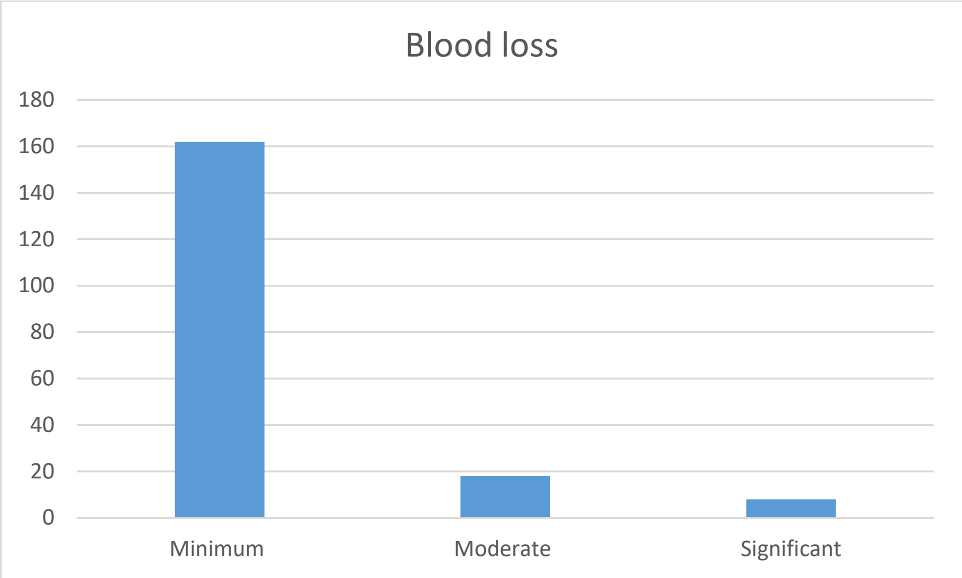


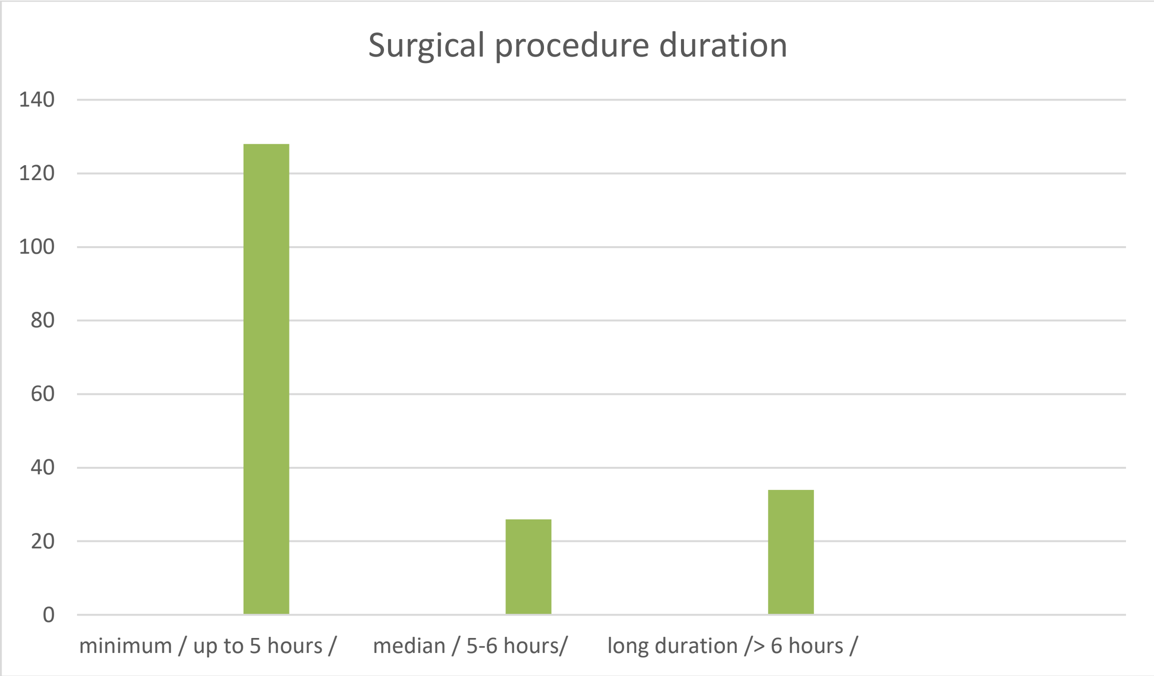
Fig. 7 – Blood loss

7. Medium hospital stay / Included the time for preoperative preparation and recovery of the nutritional status and homeostasis of patients, as well as postoperative actions for recovery from this serious surgical intervention / - 15.6 days.

8. Surgical procedure duration

Minimum / up to 5 hours / –	**128**	**68%**
Median / 5-6 hours/ –	**26**	**14%**
Long duration /> 6 hours / –	**34**	**18%**

/Fig. 8/



Фиг.8– Surgical procedure duration

With a minimum and medium duration are 82% and with a long duration are 18%

There are 34 patients with a long duration. 17 of them are VATS + L-scopia /out of 25 procedures /68%/, of 163 procedures, 17 are with open operative intervention /10%/. With the increase in the number of surgical interventions, the duration of minimally invasive operations also decreased.

Of these 34 patients	**Siebert 1-**	**6**	
	Siebert 2 -	**0**	
	Siebert 3 -	**4**	
	Distal third -	**19**	
	Middle third -	**19**	
	Cervical -	**1**	**/Fig. 9/**

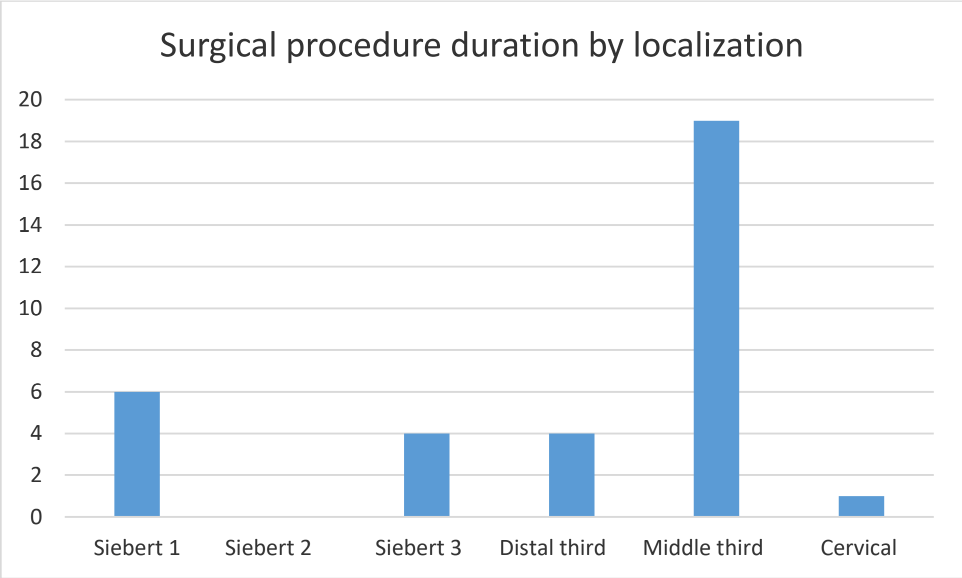


Fig. 9– Surgical procedure duration

9. By stages	**I –**	**7**	**4%**
	IIA–	**54**	**29%**
	IIB–	**19**	**10%**
	III–	**94**	**50%**
	IV–	**14**	**7%**	**/Fig. 10/**

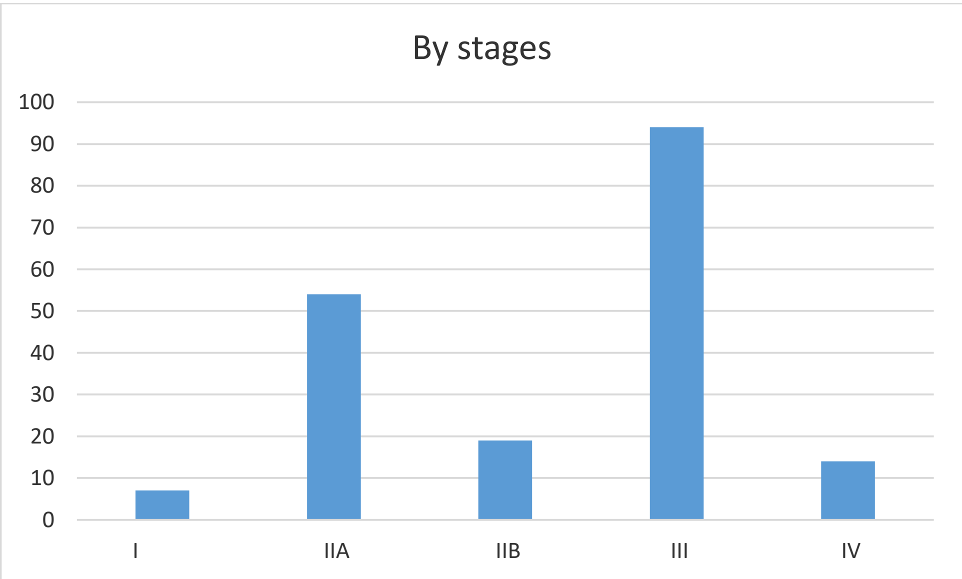


Fig. 10 – By stages

10. By histological type	**Squamous cell –**	**68**	**36,2%**	
	Adenocarcinoma –	**113**	**60.1%**	
	Leiomyosarcoma –	**1**	**0.5%**	
	Others –	**6**	**3.2%**	**/Fig. 11/**

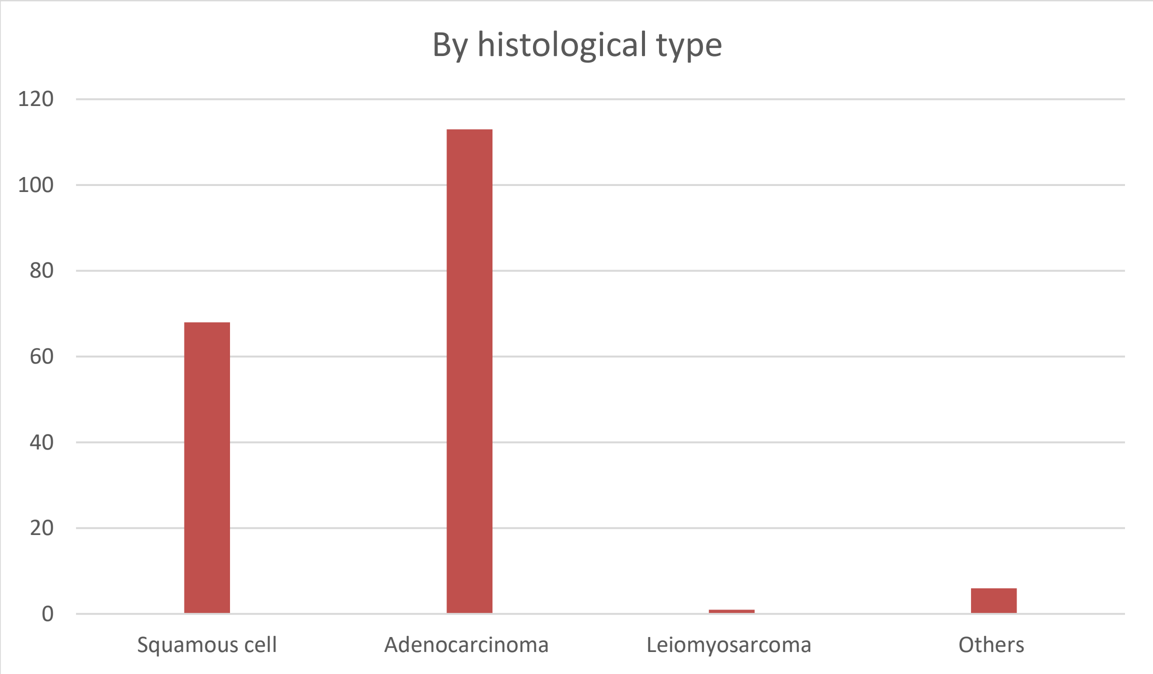


Fig. 11 – By histological type

11. By differentiation	**G1 –**	**22**	**12%**	
	G2–	**86**	**46%**	
	G3–	**80**	**42%**	**/Fig. 12/**

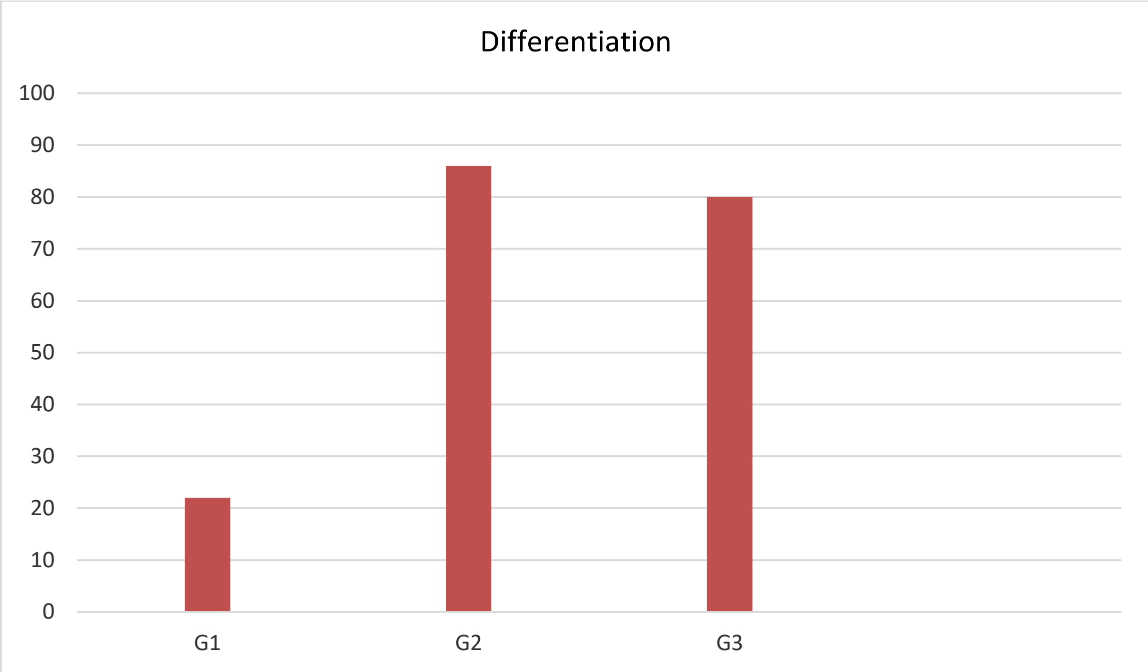


Fig. 12 – By differentiation

12. Siewert-Stein index	**0**	**–**	**65**	**34%**	
	<0,2	**–**	**13**	**7%**	
	0.2-1 –		**90**	**48%**	
	1–		**20**	**11%**	**/Fig. 13/**

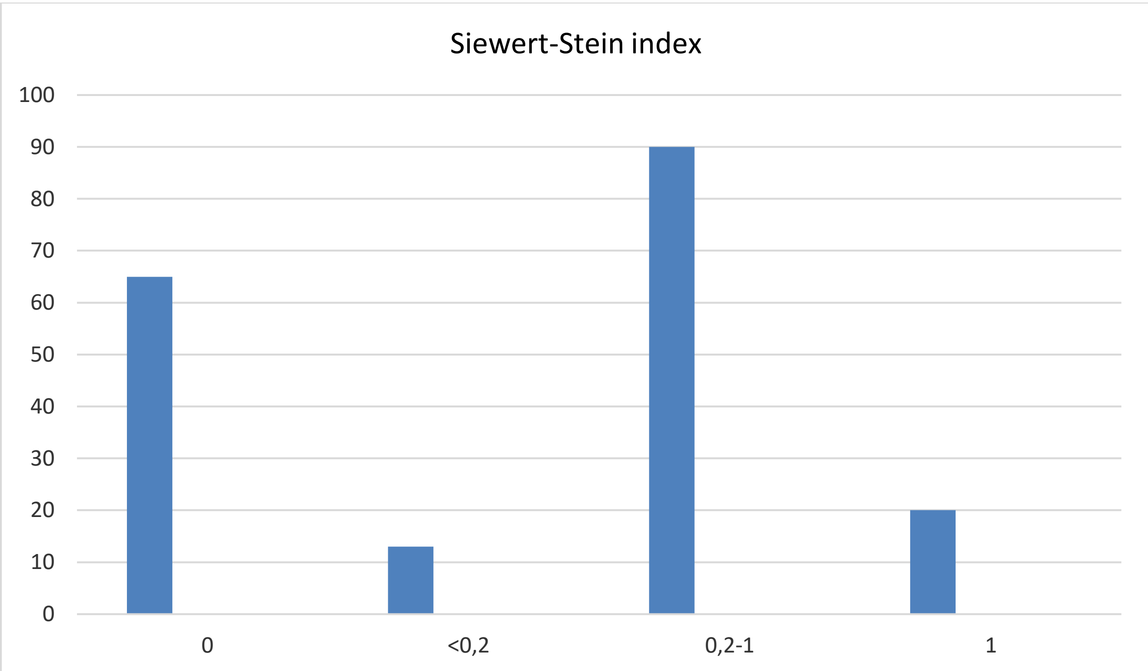


Fig. 13– Siewert– Stein index

13. Operated patients	**Siebert 1 –**	**60**	**32%**	
	Siebert 2 –	**26**	**14%**	
	Siebert 3 –	**38**	**20%**	
	Distal third –	**25**	**13%**	
	Middle third–	**33**	**18%**	
	Cervical –	**6**	**3%**	
	Total –	**188**		**/Fig. 14/**

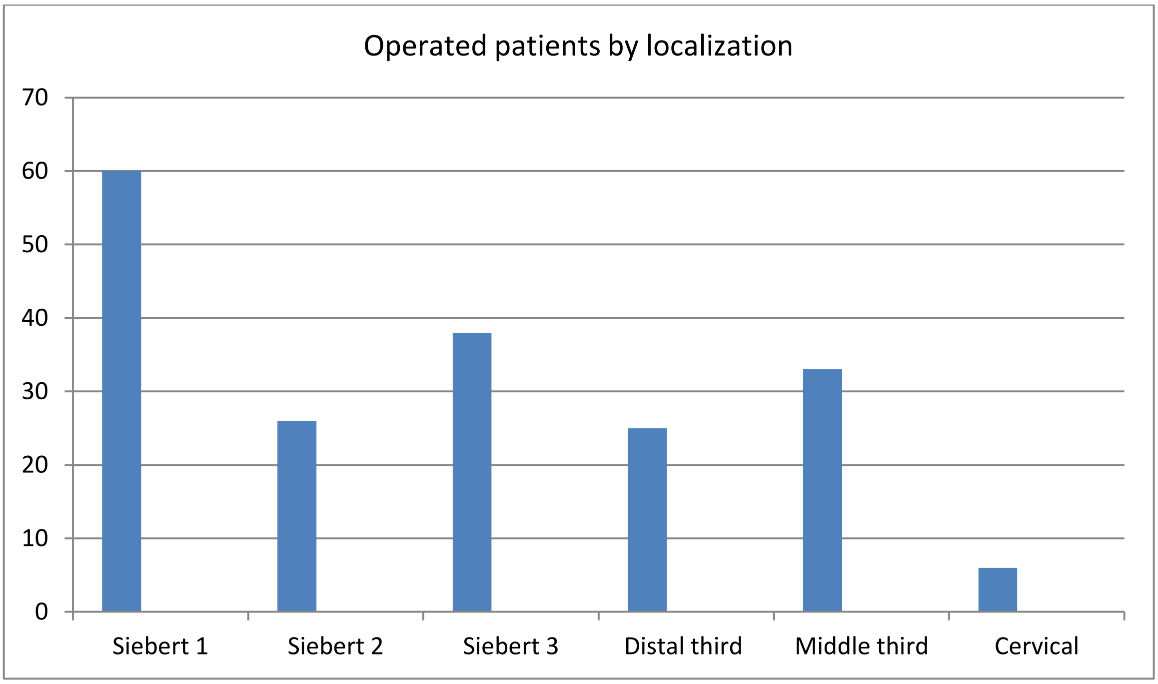


Fig. 14– Operated patients by localization

Operated patients with metastases	**Siebert 1–40 / 60 operated/**	**67%**	
	Siebert 2 – 16 /26 operated/	**62%**	
	Siebert 3 – 30 /38 operated/	**79%**	
	Distal third – 13 / 25 operated/	**52%**	
	Middle third – 22 /33 operated/	**67%**	
	Cervical – 2 /6 operated/	**33%**	
	Total – 123 /65%/		**/Fig. 15/**

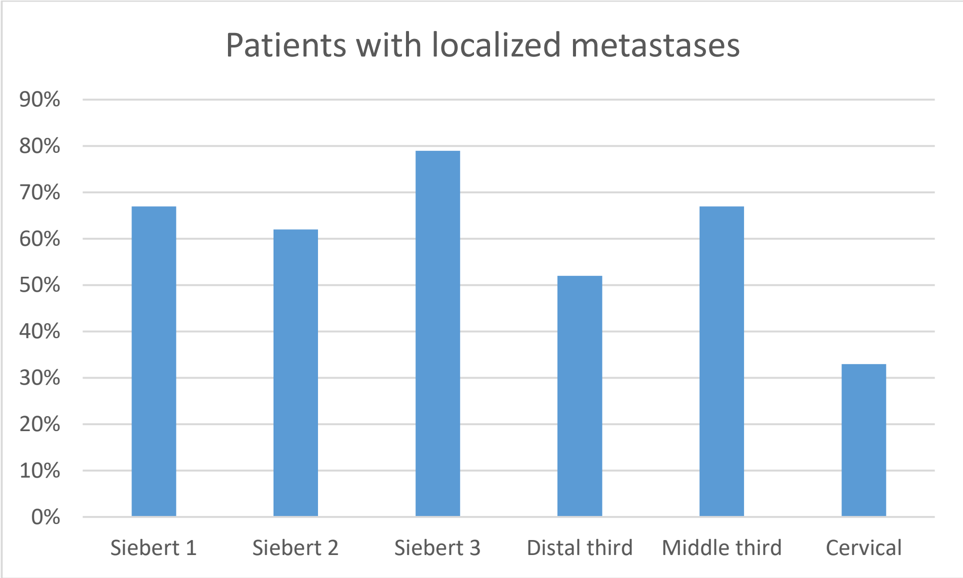


Fig. 15 – Patients with localized metastases

Operated patients with metastases	**Siebert 1– 20 / 60 operated/**	**33%**
	Siebert 2 – 10 /26 operated/	**38%**
	Siebert 3 – 8 /38 operated/	**21%**
	Distal third– 12 / 25 operated/	**48%**
	Middle third – 11 /33 operated/	**23%**
	Cervical – 4 /6 operated/	**66%**
	Total – 65 /35%/	**/Fig. 16/**

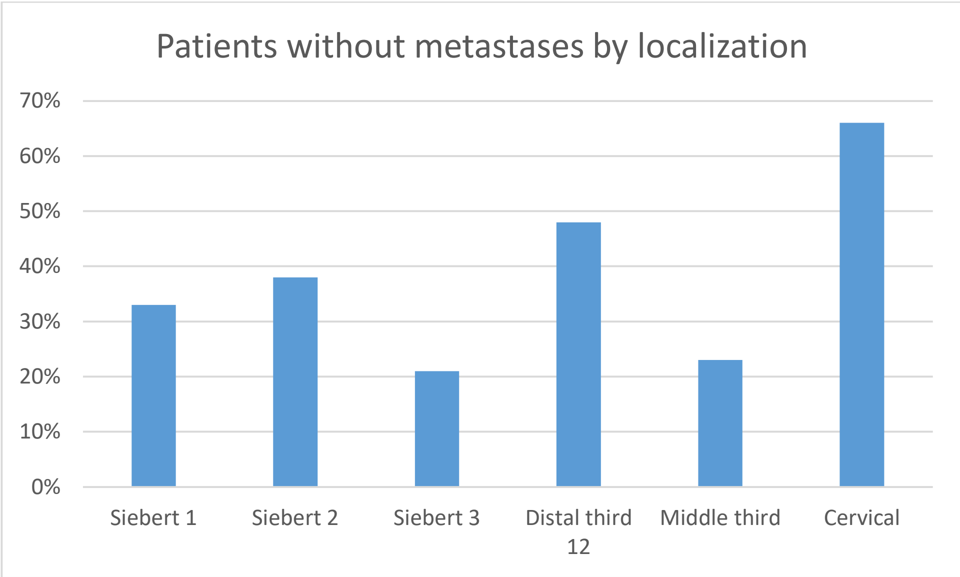
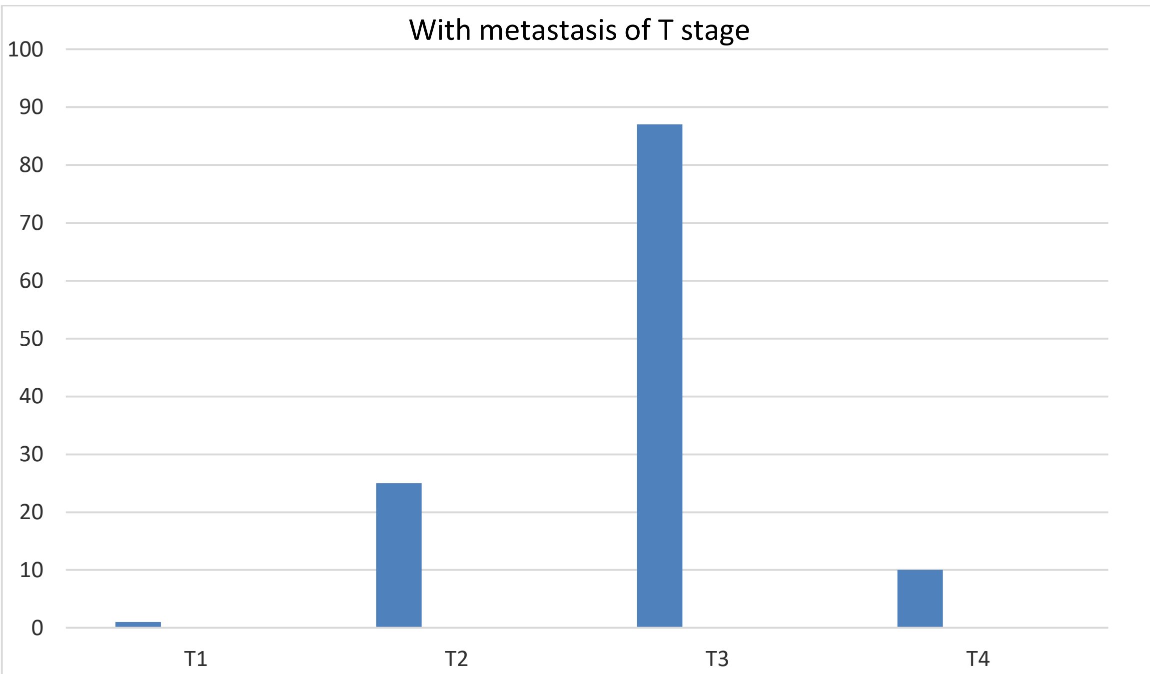


Fig. 16 – Patients without metastases by localization

14. There are 123 patients with metastases

T 1 – 1	**1%**	**N0 – 1**	**1%**	**IIB – 20**	**16%**
T 2 – 25	**20%**	**N1 – 72**	**59%**	**III – 91**	**74%**
T 3 – 87	**71%**	**N2 – 30**	**24%**	**IV – 12**	**10%**
T 4 – 10	**8%**	**N3 – 20**	**16%**	**/Fig. 17, 18/**	



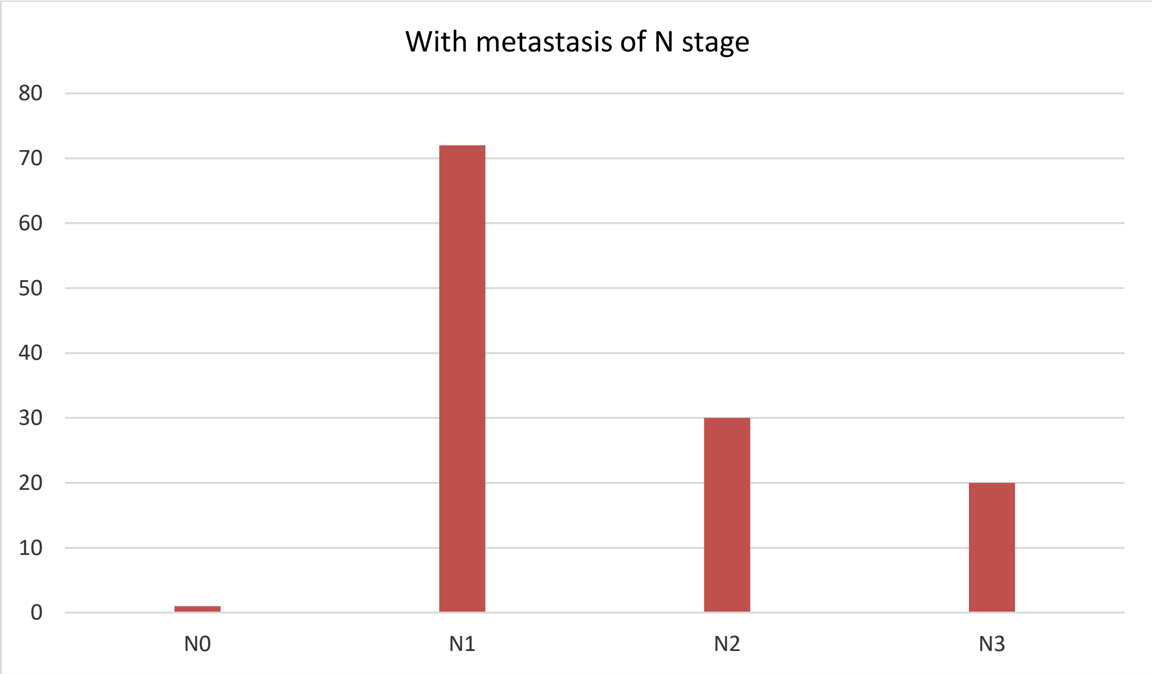


Fig. 17, 18 – With metastasis in stages T, N

15. T1, T2 with metastases

Siebert 1 – 7	**/ 40 operated/**	**18%**
Siebert 2 – 2	**/16 operated/**	**13%**
Siebert 3 – 8	**/30 operated/**	**27%**
Distal third – 3	**/ 13 operated/**	**23%**
Middle third – 5	**/22 operated/**	**23%**
Cervical – 1	**/2 operated/**	**50%**

Total – 26 /21%/ /Fig. 19/

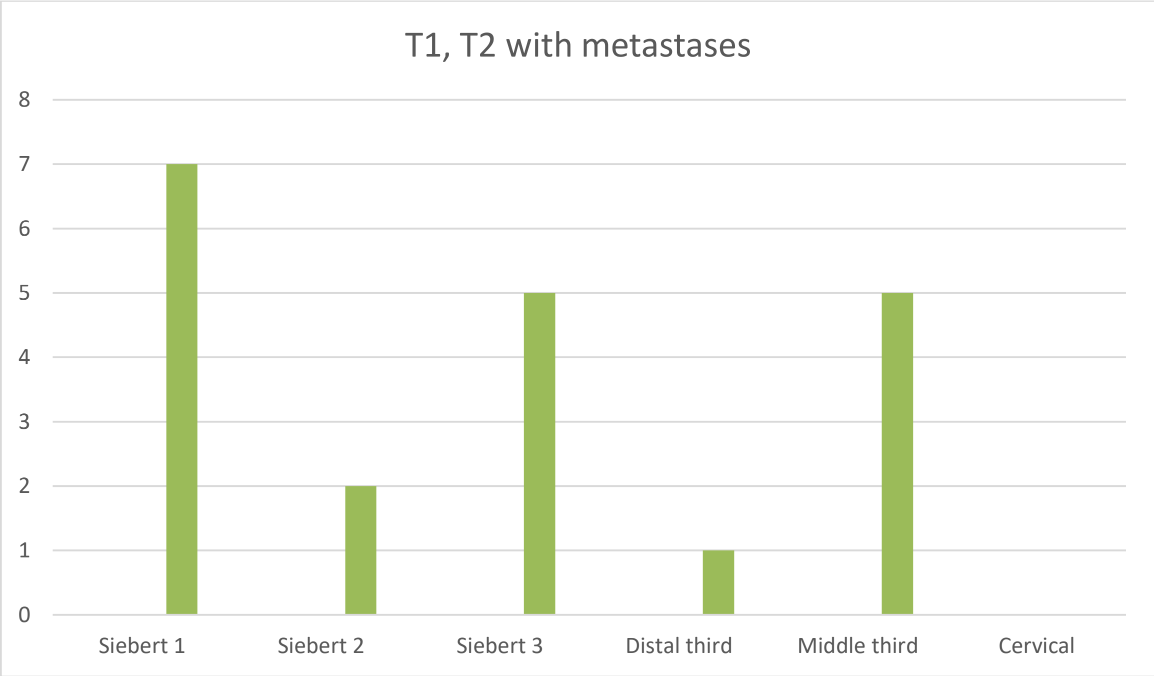


Fig. 19– T1, T2 with metastases

16. IIB with metastases	**Siebert 1 – 7 / 40 operated/ 18%**
	Siebert 2 – 2 /16 operated/ 13%
	Siebert 3 – 5 /30 operated/ 17%
	Distal third – 1 / 13 operated/ 8%
	Middle third – 5 /22 operated/ 23%
	Cervical – 0 /2 operated/ 0%
	Total – 20 /16%/ /Fig. 20/

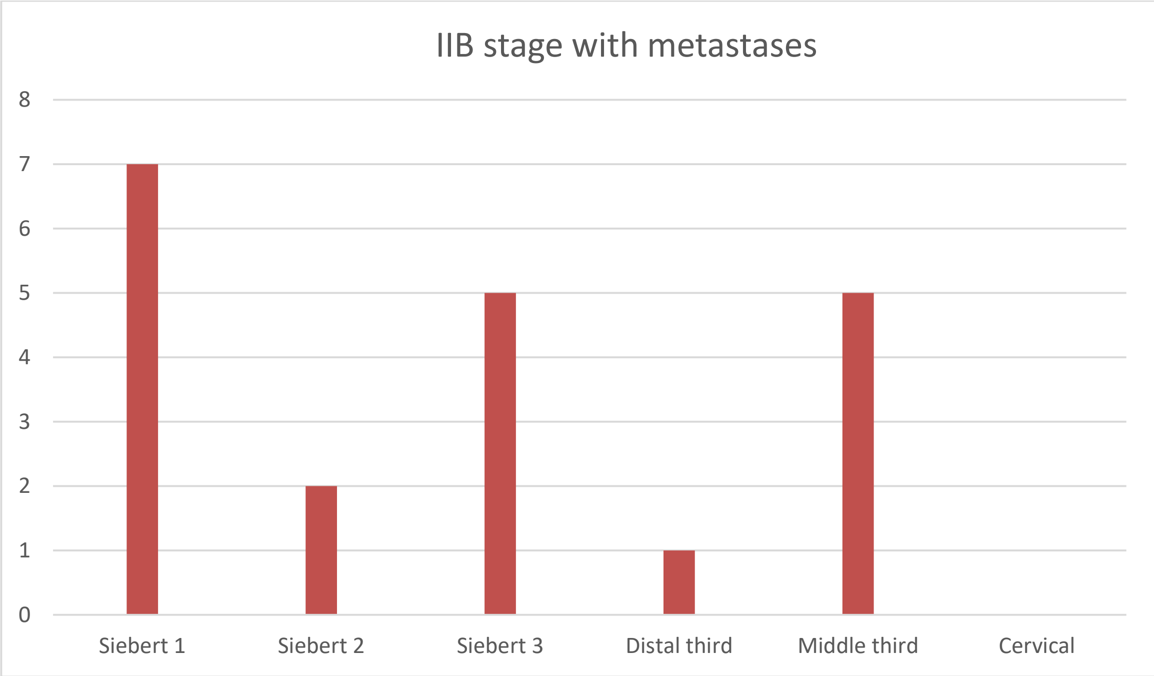


Fig. 20 – IIB with metastases

17. Total number of removed lymph nodes – 1936 /1758 with open surgical intervention + 178 with minimally invasive method/. Respectively, the surgeries are 166 with open operative intervention + 22 with minimally invasive method.

1936: 188 = 10.3 or an average of 10 lymph nodes per operation are removed.

For a minimally invasive method /178: 22 = 8 - 8 lymph nodes are removed per operation/.

For a minimally invasive method /1758: 166 = 10.6 - 10.6 lymph nodes are removed per operation/.

More lymph nodes are removed in open operative intervention - 8: 10.6 = 75% /minimally invasive 75%, open 100%/.

18. Lymph nodes by groups

Metastases in the neck area

Cervical –	**17**	**metastatic 11 /65%/**

Metastases in the thoracic cavity

Subaortic -	**21**	**metastatic 19 /90%/**
Hilar –	**29**	**metastatic 3 /10%/**
In the ligamentum pulmonary –	**38**	**metastatic 7 /18%/**

Paraesophageal - 397 metastatic 148 /37%/ /Фиг. 21/

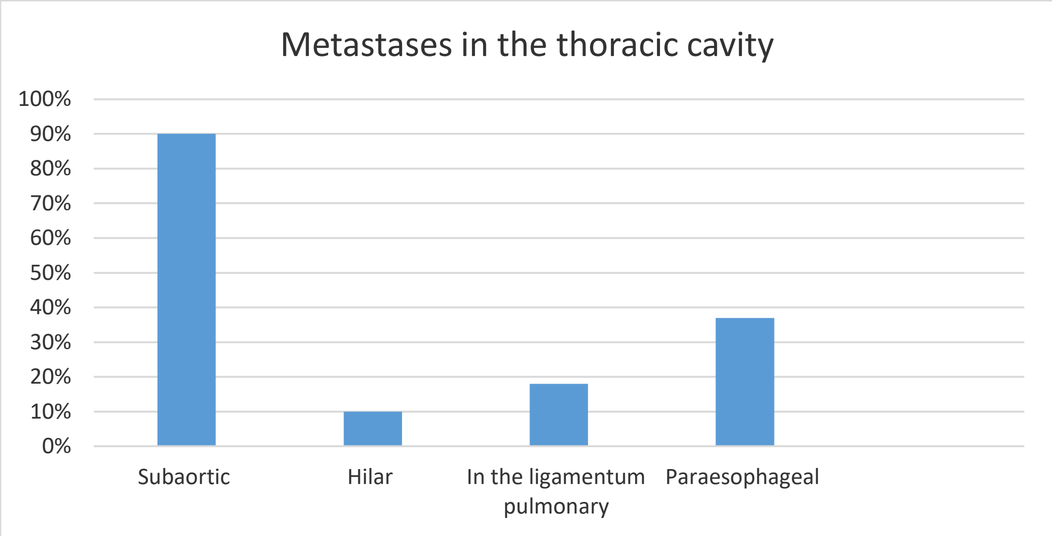


Fig. 21 - Metastases in the thoracic cavity

Metastases in the thoracic cavity

Cardia	**284 metastatic 119 /42%/**
Lymph nodes on the small curvature	**97 metastatic 27 /29%/**
Celiac lymph nodes	**236 metastatic 101 /43%/**
Other lymph nodes / hepatic, lienal /	**85 metastatic 31 /36%/ /Fig. 22/**

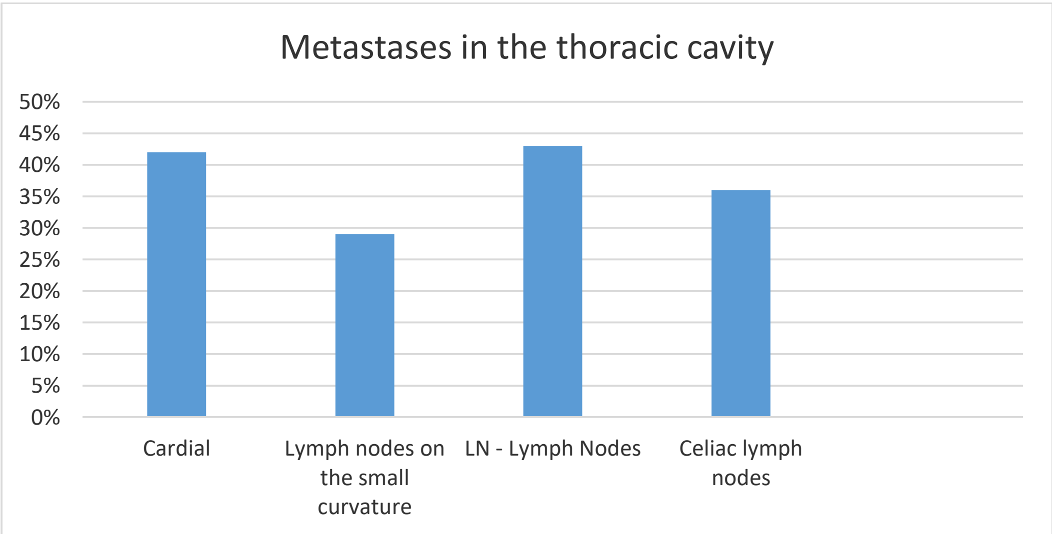


Fig. 22 – Metastases in the abdominal cavity

paratumoral metastases

paratumoral lymph nodes – 719 metastatic – 322 /45%/

19. Cavity metastasis

Patients with metastases in the thoracic cavity 58/123 have metastases / 47%

Patients with metastases in the abdominal cavity 77/123 have metastases / 63%

Patients with neck metastases 3/123 have metastases / 2%

Fig. 23

The higher overall rate is due to the fact that some patients have metastases in both cavities.

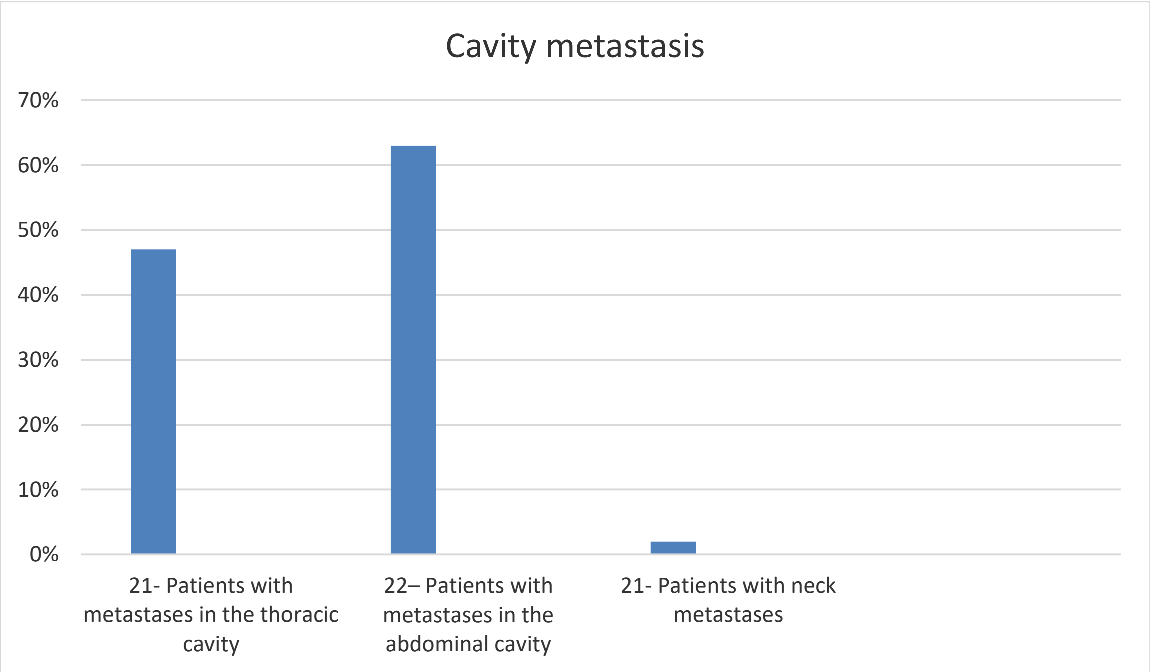


Fig. 23 - Cavity metastasis

Siebert 1 - with metastases in the thoracic cavity 15 40 operated 38%

with metastases in the abdominal cavity 23 40 operated 58%

with neck metastases 1 40 operated 3%

- In most patients, the lymphatic routes of spread are in the abdominal cavity /Fig. 24/

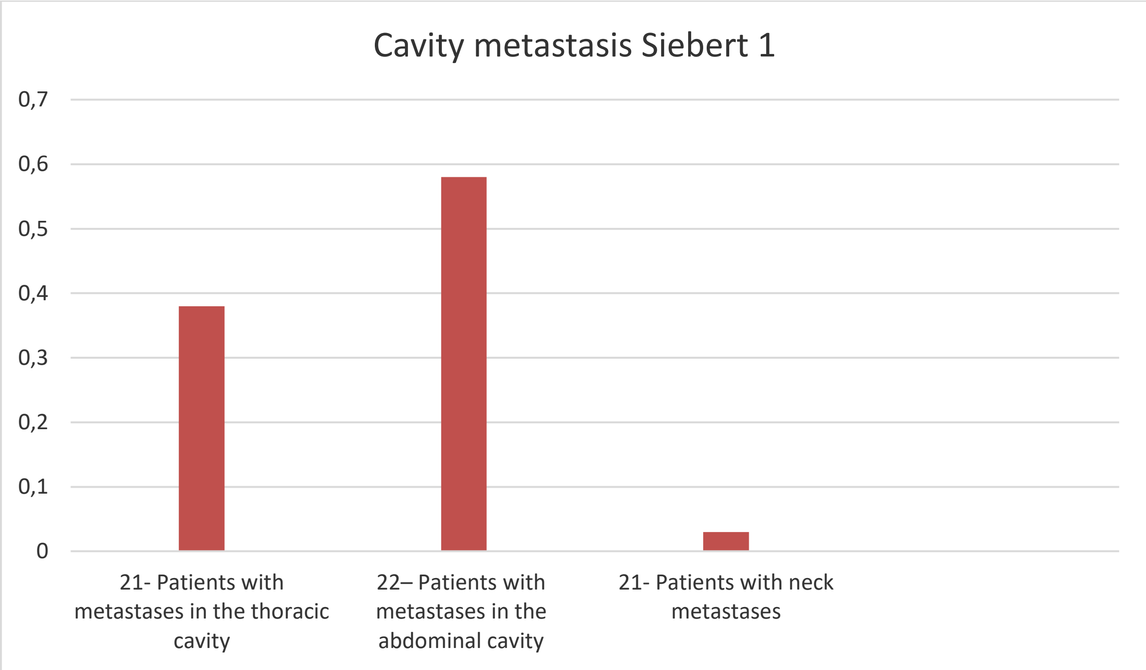


Fig. 24 - Cavity metastasis by Siebert 1

Siebert 2 - with metastases in the thoracic cavity 7 16 operated 44%

with metastases in the abdominal cavity 10 16 operated 63%

The percentages are the same as for Siebert 1 /Fig. 25/

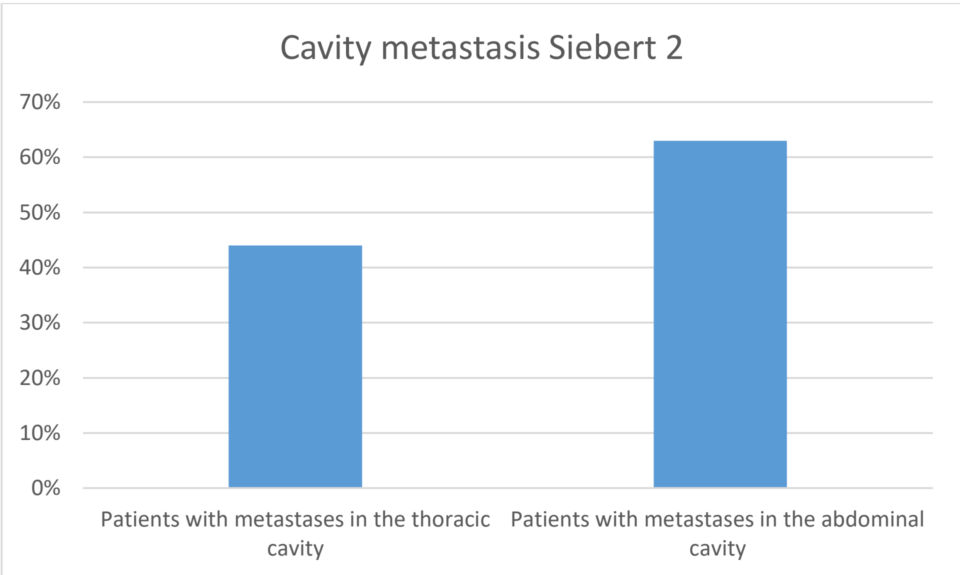


Fig. 25 - Cavity metastasis by Siebert 2

Siebert 3 - with metastases in the thoracic cavity 8 30 operated 27%

with metastases in the abdominal cavity 19 30 operated 63%

- This tendency is most pronounced in this tumour /Fig. 26/

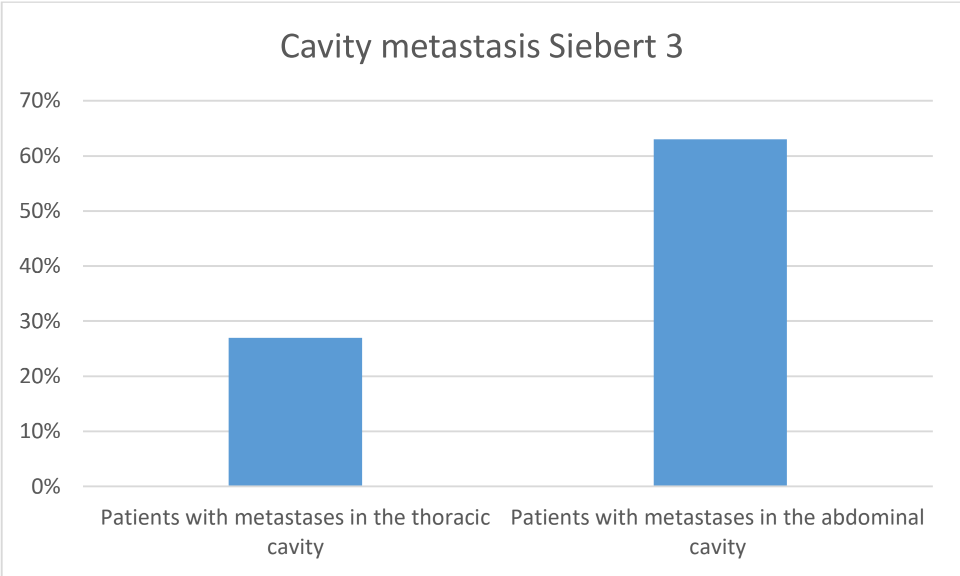


Fig. 26 - Cavity metastasis by Siebert 3

Distal third - with metastases in the thoracic cavity 10 13 operated 77%

with metastases in the abdominal cavity 10 13 operated 77%

- In the same percentage metastasizes in the thoracic and abdominal cavities /Fig.27/

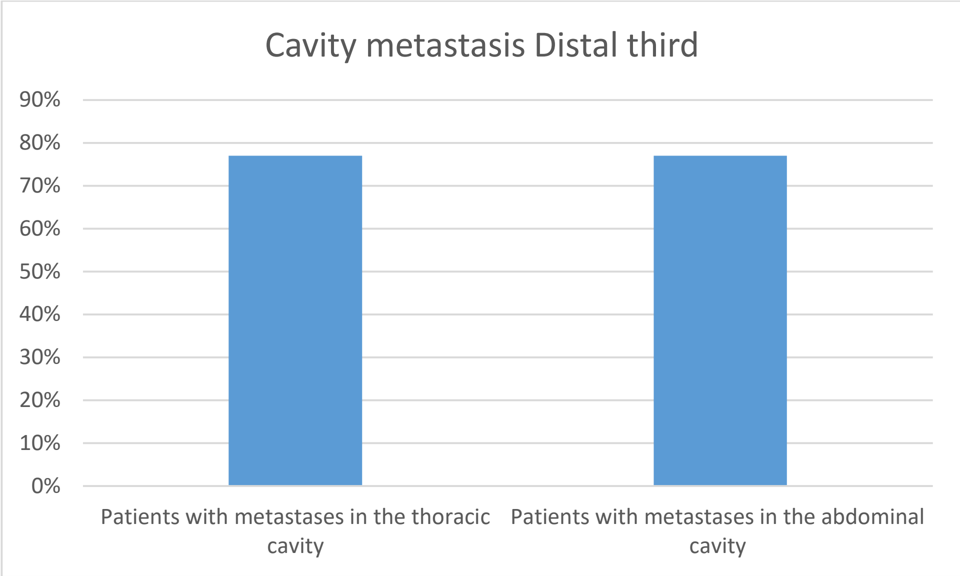


Fig. 27 - Cavity metastasis. Distal third of the oesophagus

Middle third	**with metastases in the thoracic cavity**	**15 22 operated**	**69%**
	with metastases in the abdominal cavity	**13 22 operated**	**59%**
	with neck metastases	**1 22 operated**	**5%**

- In most patients, the lymphatic routes of spread are in the abdominal cavity /Fig. 28/

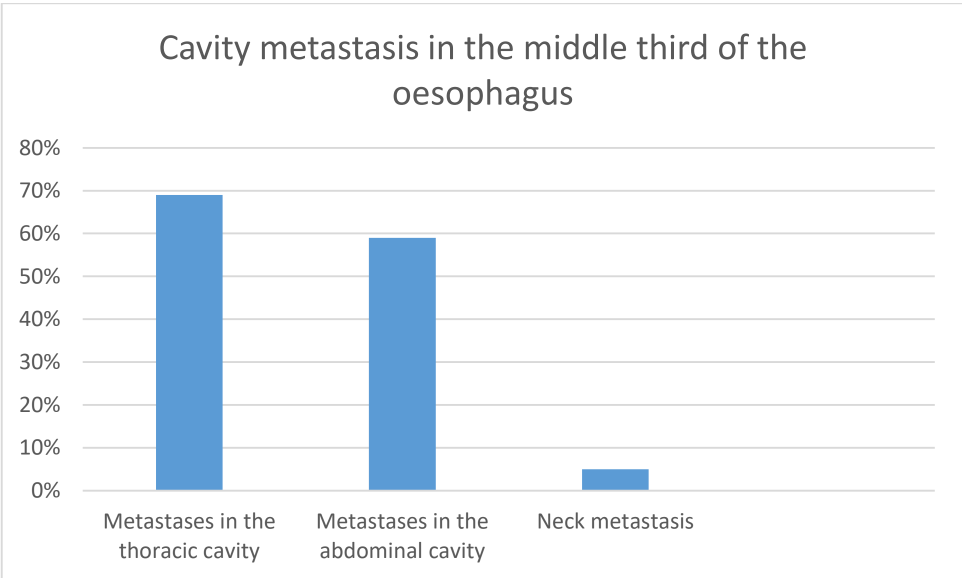


Fig. 28 - Cavity metastasis. Middle third of the oesophagus

Cervical –	**with metastases in the thoracic cavity**	**2 /2 operated/**	**100%**
	with metastases in the abdominal cavity	**2 /2 operated/**	**100%**
	with neck metastases	**1 / 2 operated/**	**50%**

- In the same percentage metastasizes in the thoracic and abdominal cavities. /Fig. 29/

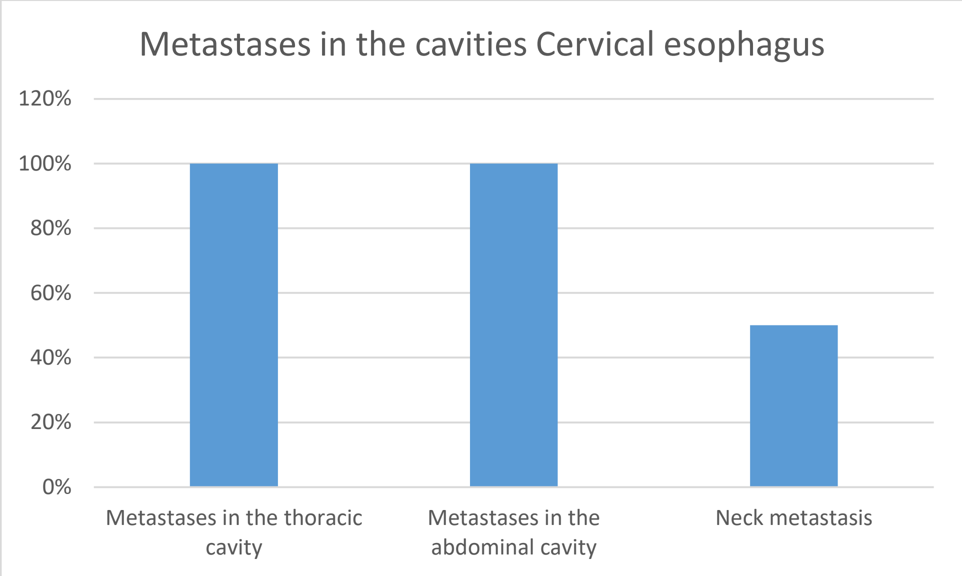


Fig. 29 - Cavity metastasis. Cervical oesophagus

20. Paratumoral metastases together with metastases in regional lymph nodes

Patients with paratumoral metastases together with metastases in regional lymph nodes 69 /127 have metastases/ 54%.

Siebert 1 –	**28 /40 operated/**	**70%**	
Siebert 2 –	**8 /16 operated/**	**50%**	
Siebert 3 –	**21 /30 operated/**	**70%**	
Distal third –	**4 / 13 operated/**	**31%**	
Middle third –	**7 /22 operated/**	**32%**	
Cervical –	**1 /2 operated/**	**50%**	**/Fig. 30/**

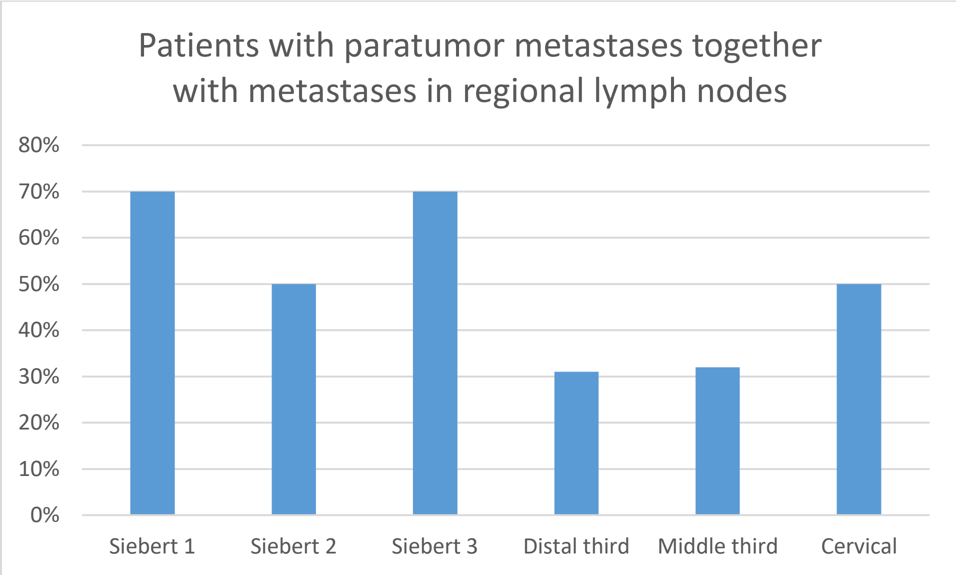


Fig. 30 – Patients with paratumoral metastases together with metastases in regional lymph nodes

Patients with metastases by location

Siebert 1 –	**13 /40 operated/**	**33%**
Siebert 2 –	**3 /16 operated/**	**19%**
Siebert 3 –	**6 /30 operated/**	**20%**
Distal third –	**1 / 13 operated/**	**8%**
Middle third –	**3 /22 operated/**	**14%**
Cervical –	**0 /2 operated/**	**0%**

/Fig. 31/

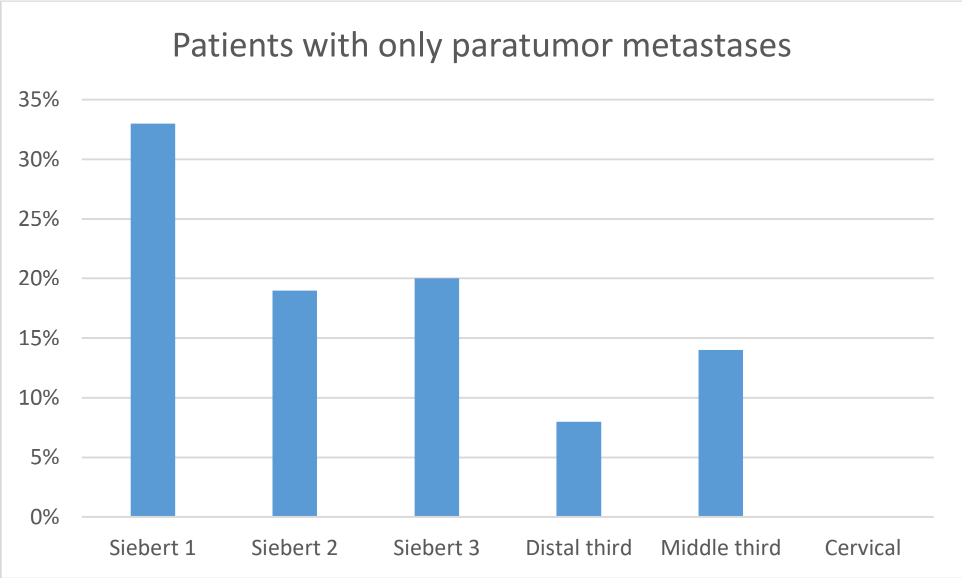


Fig. 31– Patients with only paratumoral metastases

21. Metastases by localization of the carcinoma

Siebert 1 –	**229**	**/40 operated/ average 6 metastases by patient**
Siebert 2 –	**115**	**/16 operated/ average 7 metastases by patient**
Siebert 3 –	**241**	**/30 operated/ average 8.1 metastases by patient**
Distal third –	**103**	**/13 operated/ average 7.9 metastases by patient**
Middle third –	**103**	**/22 operated/ average 5 metastases by patient**
Cervical –	**8**	**/2 operated/ average 4 metastases by patient**

/Fig. 32/

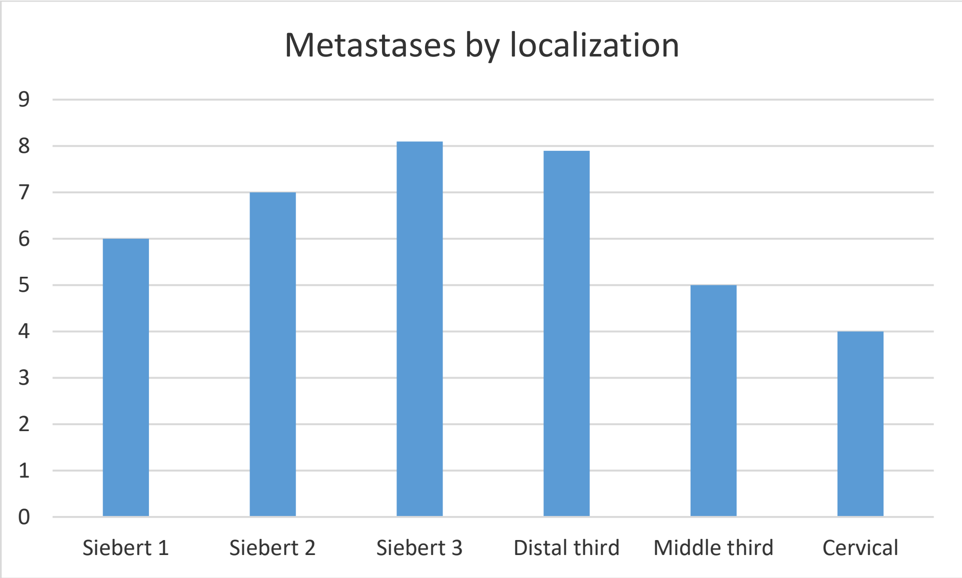


Fig. 32 – Metastases by localization

22. Paratumoral metastases by histology

Adenocarcinoma	**55**	**/113 operated/**	**49%**	
Squamous cell	**15**	**/68 operated/**	**22%**	
Mixed	**5**	**/6 operated/**	**83%**	**/Fig. 33/**

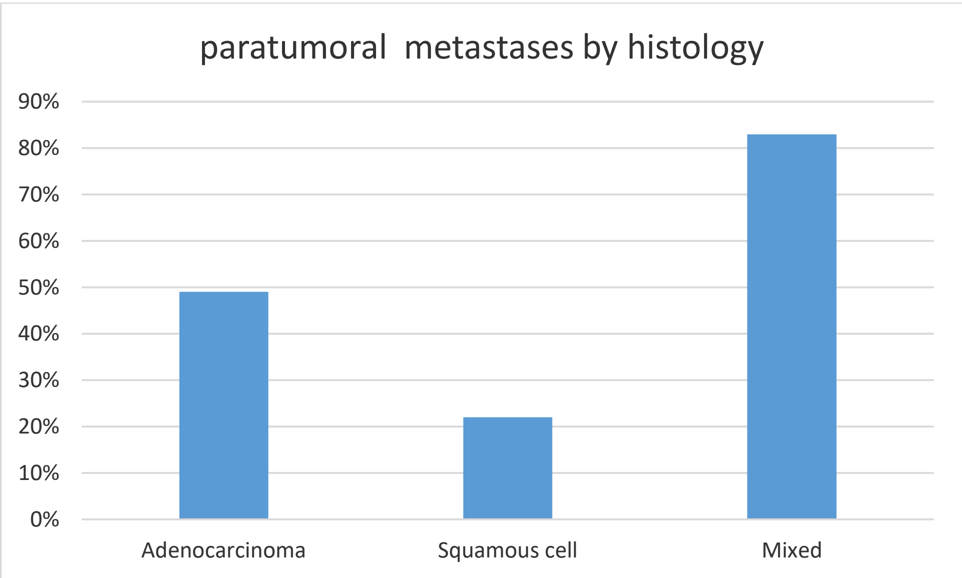


Fig. 33– Paratumoral metastases by histology

Other metastases /regional/ by histology

Adenocarcinoma	100	/113 operated/	88%	
Squamous cell	55	/68 operated/	81%	
Mixed	5	/6 operated/	83%	
Leiomyosarcoma 1	1	/1 operated/	100%	/Fig. 34/

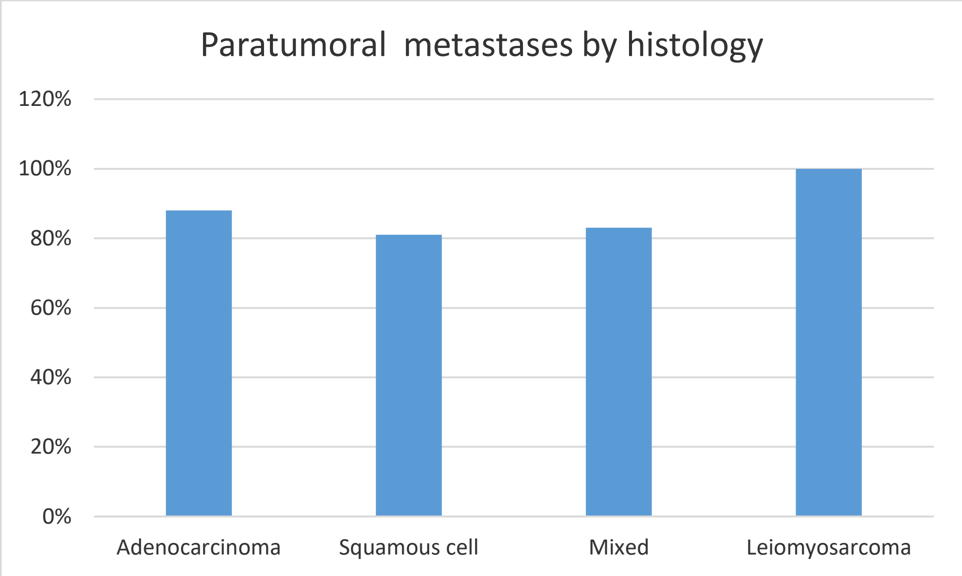


Fig. 34– Regional metastases by histology

23. Total number of removed metastatic lymph nodes by groups

Siebert 1 –	cervical	6	
	subaortic	7	
	hilar	0	
	in the ligamentum pulmonary	1	
	paraoesophagial	44	
	cardia	37	
	small curvature	3	
	celiac	38	
	other /lienal, hepatic/	13	
	paratumoral	80	/Fig. 35/

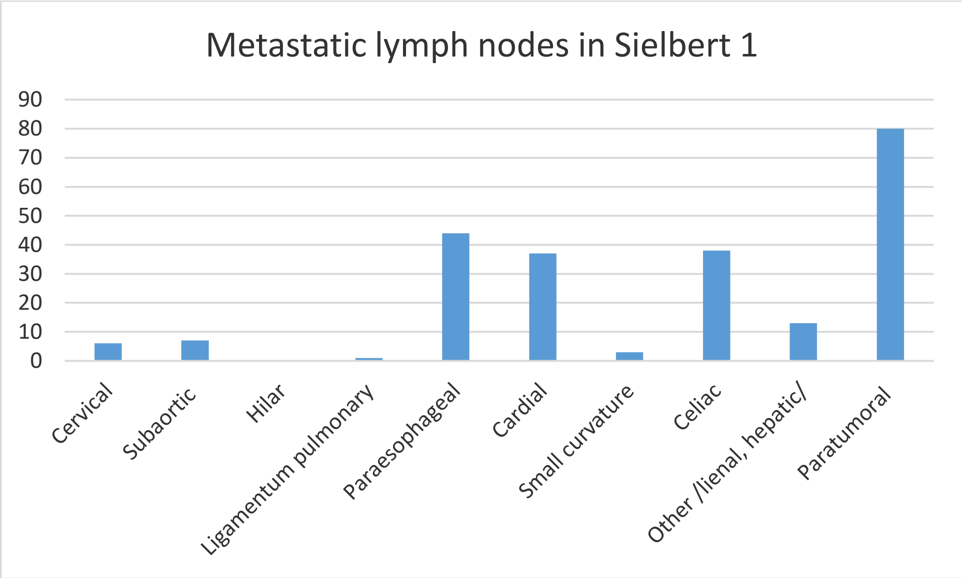


Fig. 35– Metastatic lymph nodes in Sielbert 1

Siebert 2 –	**cervical**	**0**	
	subaortic	**0**	
	hilar	**0**	
	in the ligamentum pulmonary	**1**	
	paraoesophagial	**17**	
	cardia	**20**	
	small curvature	**8**	
	celiac	**22**	
	other /lienal, hepatic/	**0**	
	paratumoral	**46**	**/Fig. 36/**

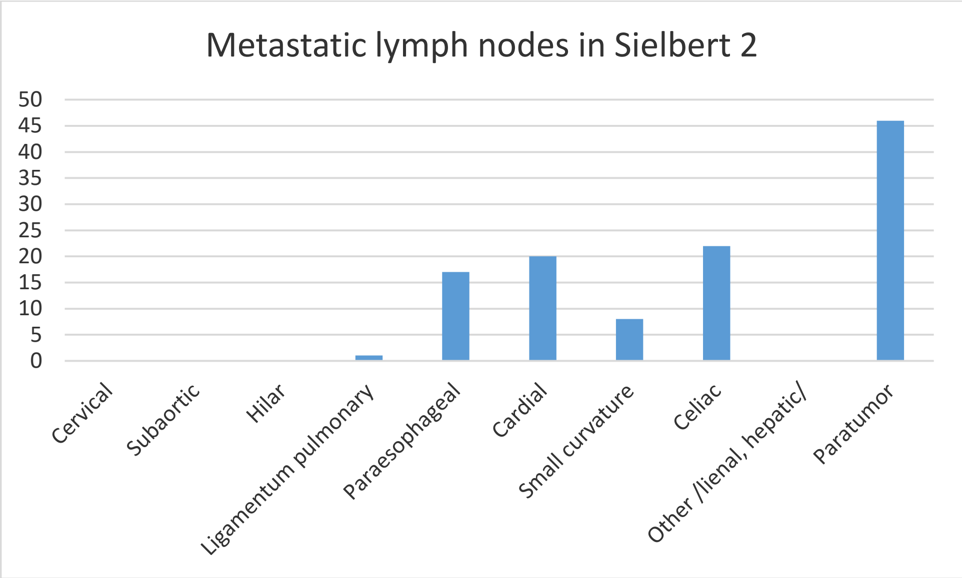


Fig. 36 – Metastatic lymph nodes in Sielbert 2

Siebert 3 –	**cervical**	**0**	
	subaortic	**7**	
	Hilar	**0**	
	in the ligamentum pulmonary	**2**	
	Paraoesophagial	**18**	
	Cardia	**38**	
	small curvature	**11**	
	Celiac	**20**	
	Other /lienal, hepatic/	**16**	
	Paratumor	**129**	**/Fig. 37/**

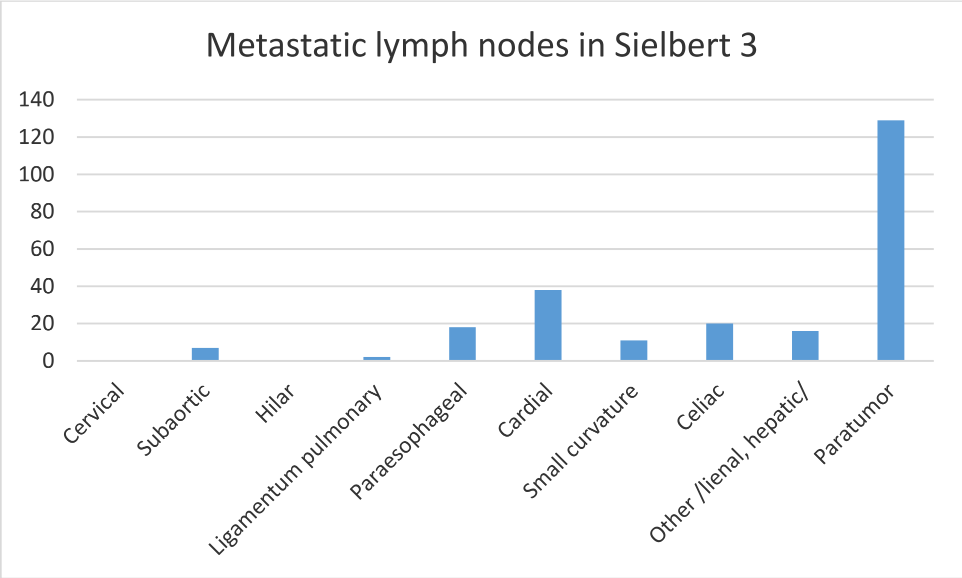


Fig. 37 – Metastatic lymph nodes in Sielbert 3

Distal third -	**cervical**	**0**	
	subaortic	**1**	
	hilar	**4**	
	in the ligamentum pulmonary	**0**	
	Paraoesophagial	**31**	
	Cardia	**16**	
	small curvature	**7**	
	celiac	**10**	
	other /lienal, hepatic/	**0**	
	paratumoral	**29**	**/Fig. 38/**

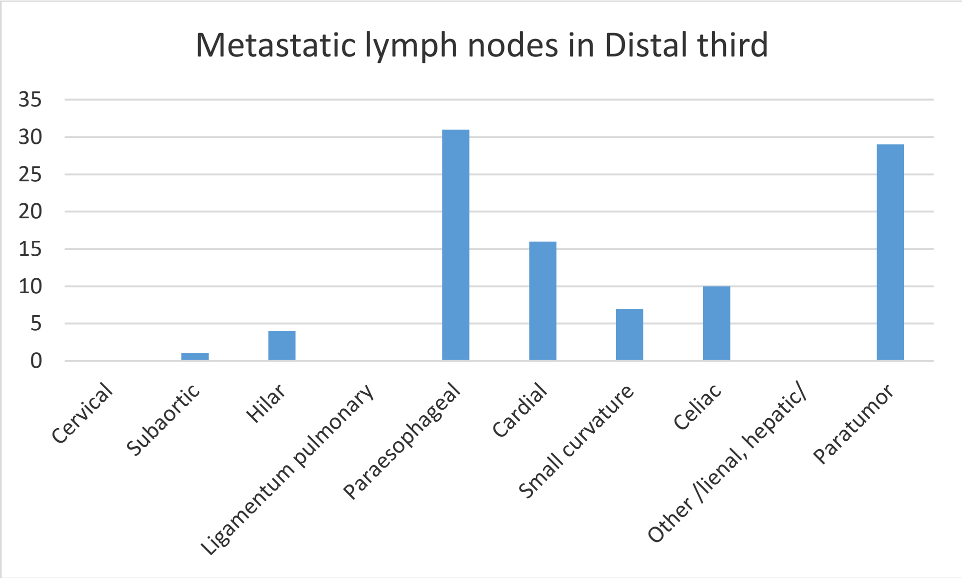


Fig. 38 – Metastatic lymph nodes in Distal third

Distal third -	**cervical**	**2**	
	subaortic	**1**	
	hilar	**3**	
	in the ligamentum pulmonary	**2**	
	caraoesophagial	**37**	
	cardia	**11**	
	small curvature	**0**	
	celiac	**16**	
	other /lienal, hepatic/	**2**	
	paratumoral	**29**	**/Fig. 39/**

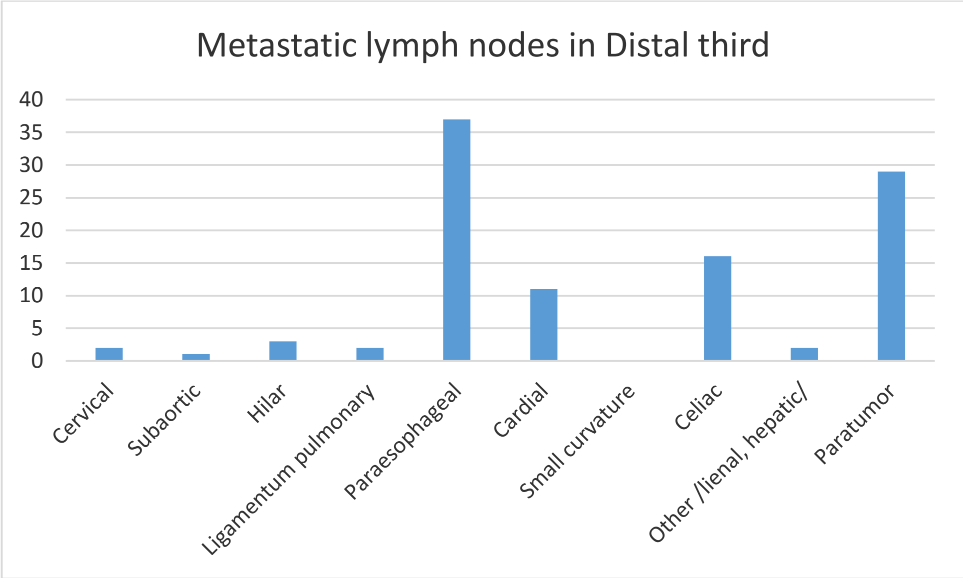


Fig. 39 – Metastatic lymph nodes in the Middle third

cervical -	**3**	
subaortic	**0**	
hilar	**0**	
in the ligamentum pulmonary	**0**	
caraoesophagial	**2**	
cardia	**1**	
small curvature	**0**	
celiac	**1**	
other /lienal, hepatic/	**0**	
paratumor	**1**	**/Fig. 40/**

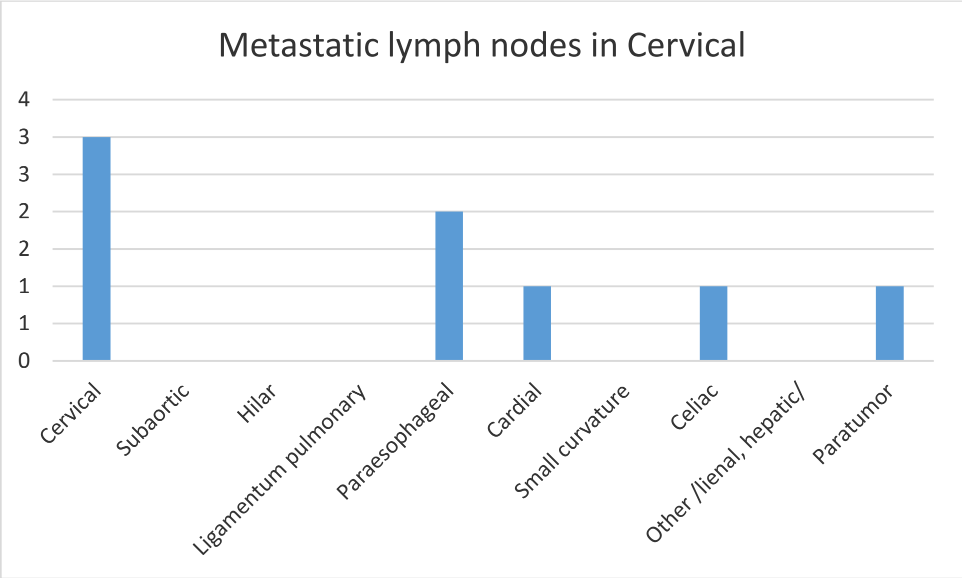


Fig. 40 – Metastatic lymph nodes in Cervical

24. Average number of metastases in the regional lymph nodes by group. In these cases, lymphatic dissection is mandatory, as they are most often subject of metastases.

Siebert 1 –	**Cervical**	**6**	**/ 40 operated/**
	Subaortic	**7**	**/40 operated/**
	Hilar	**0**	**/40 operated/**
	In the ligamentum pulmonary	**1**	**/40 operated/**
	Paraesophageal	**44**	**/40 operated/**
	Cardial	**37**	**/40 operated/**
	Small curvature	**3**	**/40 operated/**
	Celiac	**38**	**/40 operated/**
	Other /lienal, hepatic/	**13**	**/40 operated/**
	paratumoral	**80**	**/40 operated/**

/Fig. 41/

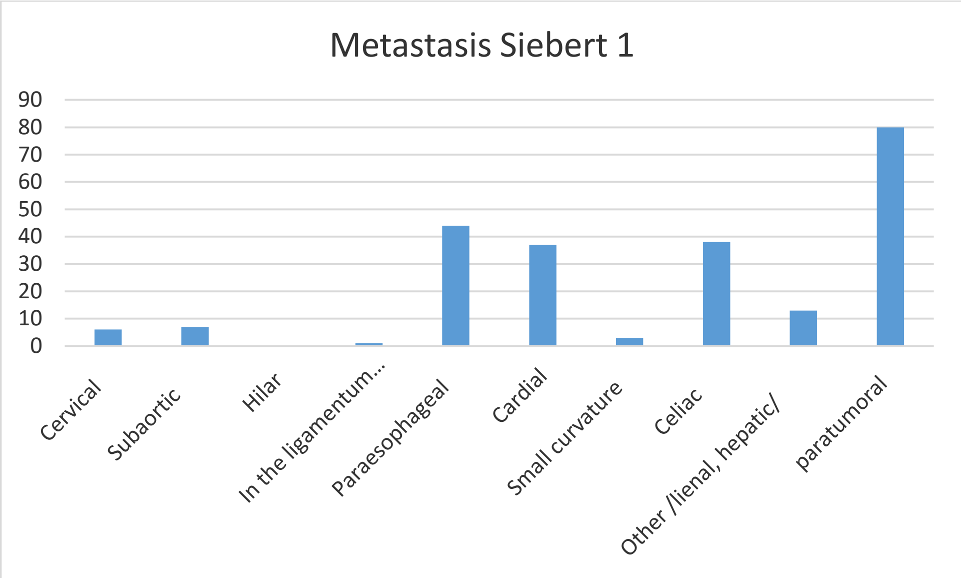


Fig. 41 – Metastasis Siebert 1

MANDATORY DISSECTION PERFORMED IN PARATUMORAL, PARAESOPHAGEAL, CARDIAL, CELIAC AREAS

Siebert 2 –	**Cervical**	**0**	**/ 16 operated/**
	Subaortic	**0**	**/16 operated/**
	Hilar	**0**	**/16 operated/**
	In the ligamentum pulmonary	**1**	**/16 operated/**
	Paraesophageal	**17**	**/16 operated/**
	Cardial	**20**	**/16 operated/**
	Small curvature	**8**	**/16 operated/**
	Celiac	**22**	**/16 operated/**
	Other /lienal, hepatic/	**0**	**/16 operated/**
	paratumoral	**46**	**/16 operated/ /Fig. 42/**

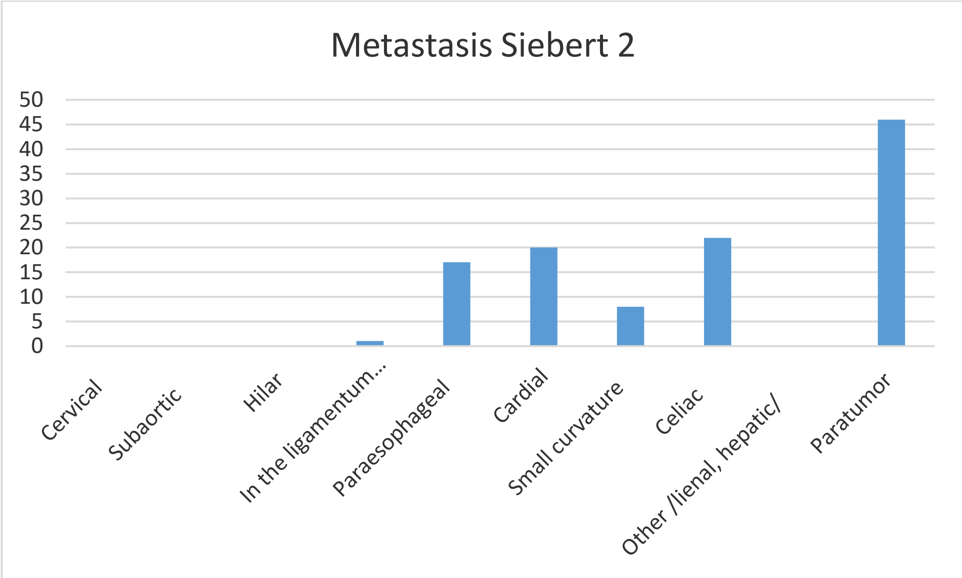


Fig. 42 – Metastasis Siebert 2

MANDATORY DISSECTION PERFORMED IN PARATUMOR, PARAESOPHAGEAL, CARDIAL, CELIAC AREAS

Siebert 3 –	**Cervical**	**0**	**/ 30 operated/**
	Subaortic	**7**	**/30 operated/**
	Hilar	**0**	**/30 operated/**
	In the ligamentum pulmonary	**2**	**/30 operated/**
	Paraesophageal	**18**	**/30 operated/**
	Cardial	**38**	**/30 operated/**
	Small curvature	**11**	**/30 operated/**
	Celiac	**20**	**/30 operated/**
	Other /lienal, hepatic/	**16**	**/30 operated/**
	paratumoral	**129**	**/30 operated/ /Fig. 43/**

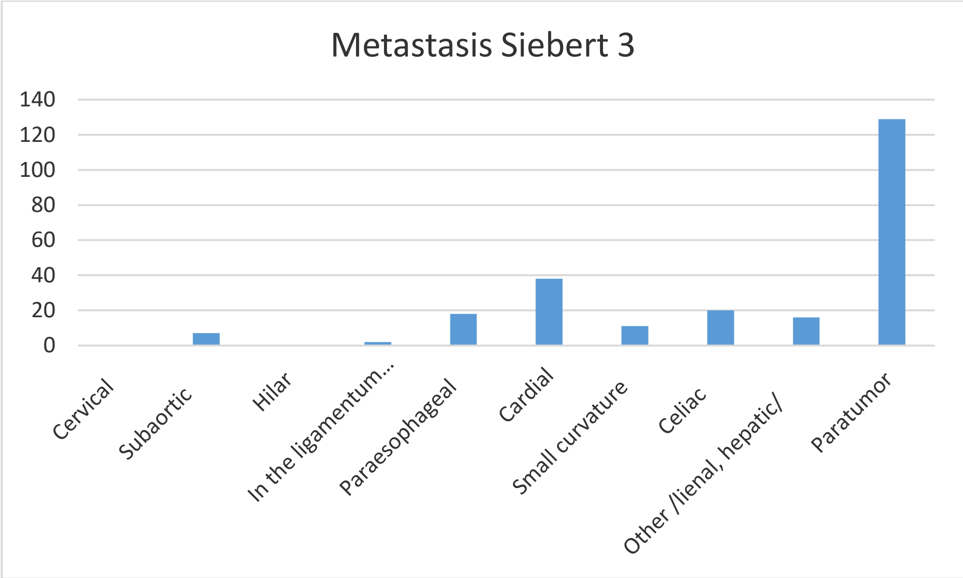


Fig. 43– Metastasis Siebert 3

MANDATORY DISSECTION PERFORMED IN PARATUMORAL, CARDIAL AREAS

Distal third –	**Cervical**	**0 /13 operated/**
	Subaortic	**1 /13 operated/**
	Hilar	**4 /13 operated/**
	In the ligamentum pulmonary	**0 /13 operated/**
	Paraesophageal	**31 /13 operated/**
	Cardial	**16 /13 operated/**
	Small curvature	**7 /13 operated/**
	Celiac	**10 /13 operated/**
	Other /lienal, hepatic/	**0 /13 operated/**
	paratumoral	**29 /13 operated/**

/Fig. 44/

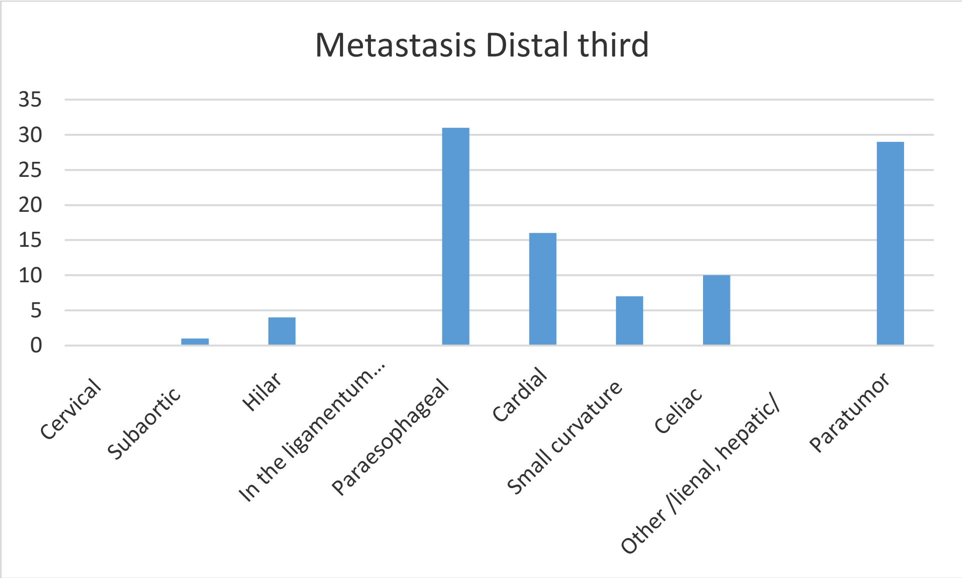


Fig. 44– Metastasis Distal third

MANDATORY DISSECTION PERFORMED IN PARATUMORAL, PARAESOPHAGEAL, CARDIAL AREAS

Middle third –	**Cervical**	**2**	**/ 22 operated/**
	Subaortic	**1**	**/22 operated/**
	Hilar	**3**	**/22 operated/**
	In the ligamentum pulmonary	**2**	**/22 operated/**
	Paraesophageal	**37**	**/22 operated/**
	Cardial	**11**	**/22 operated/**
	Small curvature	**0**	**/22 operated/**
	Celiac	**16**	**/22 operated/**
	Other /lienal, hepatic/	**2**	**/22 operated/**
	Paratumor	**29**	**/22 operated/**

/Fig. 45/

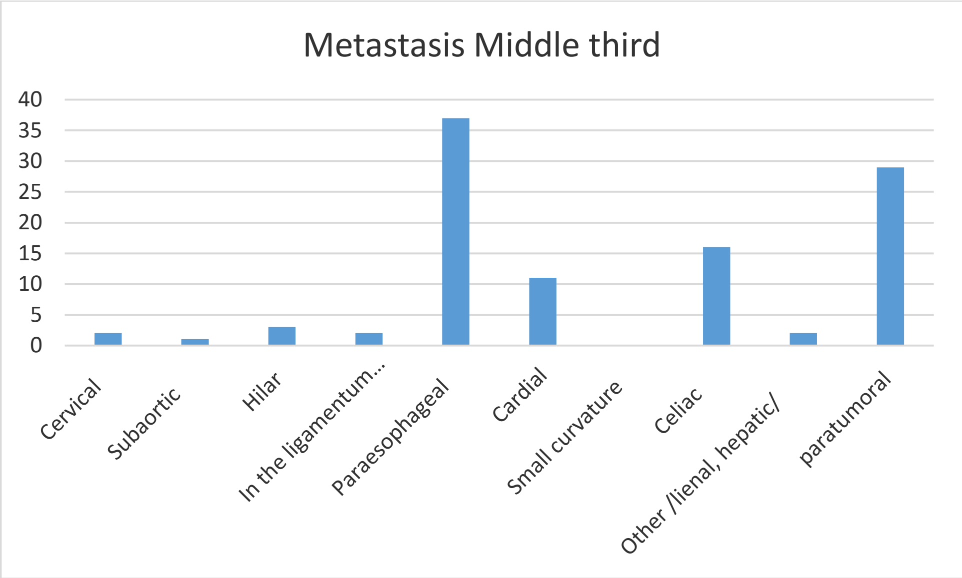


Fig. 45 – Metastasis Middle third

MANDATORY DISSECTION PERFORMED IN PARATUMORAL, PARAOESOPHAGEAL AREAS

Middle third –	**Cervical**	**3**	**/ 2 operated/**
	Subaortic	**0**	**/2 operated/**
	Hilar	**0**	**/2 operated/**
	In the ligamentum pulmonary	**0**	**/2 operated/**
	Paraesophageal	**2**	**/2 operated/**
	Cardial	**1**	**/2 operated/**
	Small curvature	**0**	**/2 operated/**
	Celiac	**1**	**/2 operated/**
	Other /lienal, hepatic/	**0**	**/2 operated/**
	Paratumor	**1**	**/2 operated/**

/Fig. 46/

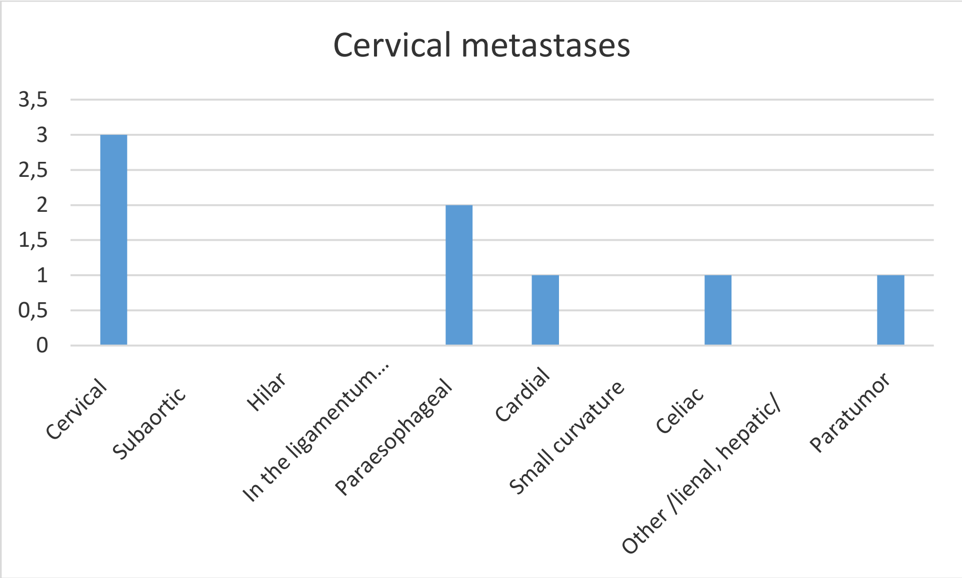


Fig. 46 - Cervical metastases

MANDATORY DISSECTION PERFORMED IN CERVICAL, PARAESOPHAGEAL AREAS

25. Highest metastatic rate by lymph node groups

CERVICAL LYMPH NODES - CANCER OF THE CERVICAL OESOPHAGUS /100%/

/We also dissected in the middle third and Siebert 1/

SUBAORTAL LYMPH NODES - SIEBERT CANCER 3 /23%/

/We also dissected in Siebert 1, lower and middle third /

HYLUSUS LYMPH NODES - LOWER THIRD CANCER / 33%/

/We also dissected in the middle third/

LYMPH NODES IN PULMONAL LIGAMENT - MIDDLE THIRD CANCER /9%/

/We also dissected in Siebert 1, 2, 3/

PARAESOPHAGEAL LYMPH NODES - LOWER THIRD CARCINOMA /100%/

/We have dissected in all types/

CARDIAL LYMPH NODES - SIEBERT CANCER 3 /100% /

/We have dissected in all types/

LYMPH NODES IN THE SMALL CURVE - CANCER OF THE LOWER THIRD /54%/

/We also dissected in Siebert 1, 2, 3/

OTHERS LYMPH NODES - SIEBERT CANCER 3 /53% /

/We also dissected in Siebert 1, middle third/

CELIAC LYMPH NODES - SIEBERT 2 /100%/

/We have dissected in all types/

PARATUMORAL LYMPH NODES - SIEBERT 3 /100%/

/We have dissected in all types/

These are metastases by groups of lymph nodes, by type of tumour localization and by the highest frequency of localization.

26. New indices

We apply the index of lymph node ratio, introduced by Siebert. We use the INDEX OF IMMEDIATE POSTOPERATIVE SURVIVAL /the ratio is the same - the ratio of the removed metastatic lymph nodes compared to the total number of removed lymph nodes of the operated patients/. We determine the index of the patients who have no postoperative complications and have not died in the hospital.

Index	**0**	**36**
	0,1-0,2	**8**
	0,2-0,3	**10**
	0,3-0,4	**3**
	0,4-0,5	**2**
	0,5-0,6	**6**
	0,6-0,7	**6**
	0,7-0,8	**5**
	0,8-0,9	**4**
	0,9-1	**16**

In total 96 patients

Up to 0.3 are 54 patients / 56% /

INDEX OF IMMEDIATE POSTOPERATIVE SURVIVAL UP TO 0.3

We also introduce an INDEX OF POSTOPERATIVE COMPLICATIONS - we do it in the same way, taking into account operated patients with postoperative complications who have not died.

0	**18**
0,1-0,2	**2**
0,2-0,3	**1**
0,3-0,4	**9**
0,4-0,5	**3**
0,5-0,6	**4**
0,6-0,7	**3**
0,7-0,8	**3**
0,8-0,9	**0**
0,9-1	**3**

In total 46 patients

Up to 0.4 are 30 patients /65%/

INDEX OF IMMEDIATE POSTOPERATIVE SURVIVAL UP TO 0,4

Similarly, taking into account operated patients with postoperative complications who have died.

0	**8**
0,1-0.2	**4**
0,2-0.3	**1**
0,3-0.4	**3**
0,4-0.5	**4**
0,5-0.6	**2**
0,6-0.7	**1**

0,7-0.8	**3**
0,8-0.9	**3**
0,9-1	**3**

AN EVEN DISTRIBUTION OF PATIENTS IS OBSERVED AND WE CANNOT INTRODUCE AN INDEX, DUE TO THE FACT THAT PATIENTS HAVE DIFFERENT ACCOMPANYING DISEASES.

27. Metastases in 2 cavities

Metastases in the thoracic cavity have 45 patients /110 operated with metastases/ - 37%, i.e. every third patient has metastases in both cavities.

Siebert 1 –	**13 /40 operated/**	**33%**	
Siebert 2 –	**6 /16 operated/**	**38%**	
Siebert 3 –	**7 /30 operated/**	**23%**	
Distal third –	**7 / 13 operated/**	**54%**	
Middle third –	**10 /22 operated/**	**45%**	
Cervical –	**2 /2 operated/**	**100%**	**/Fig. 47/**

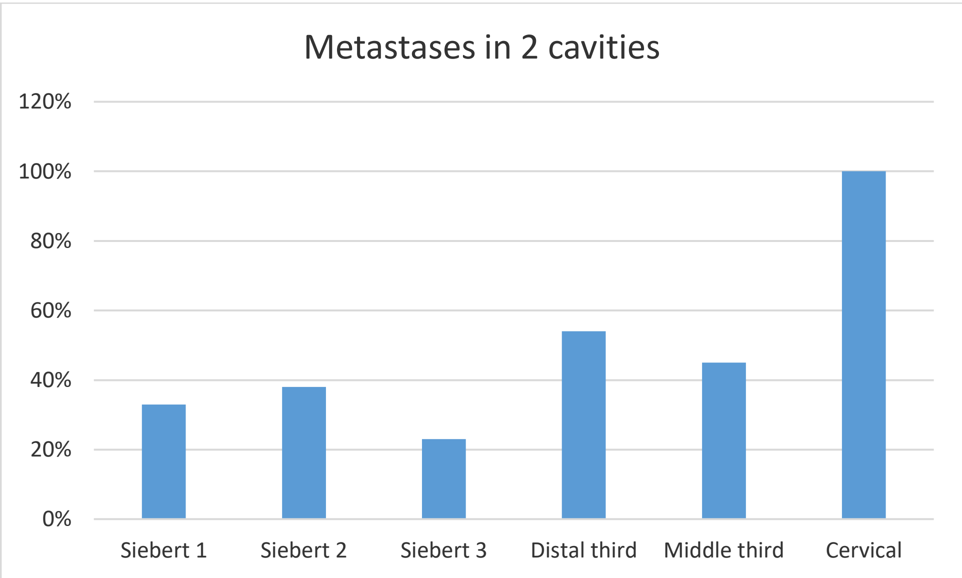


Fig. 47– Metastases in 2 cavities

In this series of patients from all 6 tumour localizations we had metastases in both areas.

Of these 45 patients with metastases in both cavities

N 1 – 22 / 49%/

N 2 – 12 / 27%/

N 3 – 11 / 24%/ /Fig. 48/

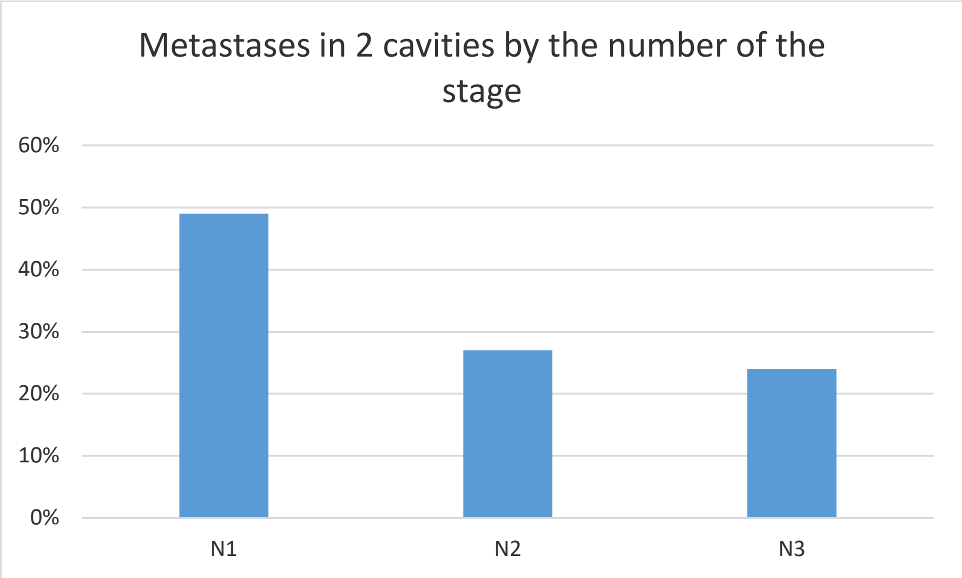


Fig. 48– Metastases in 2 cavities by the number of the stage

- The detection of 2 metastatic lymph nodes can be in both cavities /chest and abdomen/, which determines the high frequency of "skipping metastases" and the extreme aggressiveness of the tumour.

IIB– 5 /11%/

III– 32 /71%/

IV– 8 /18%/ /Fig. 49/

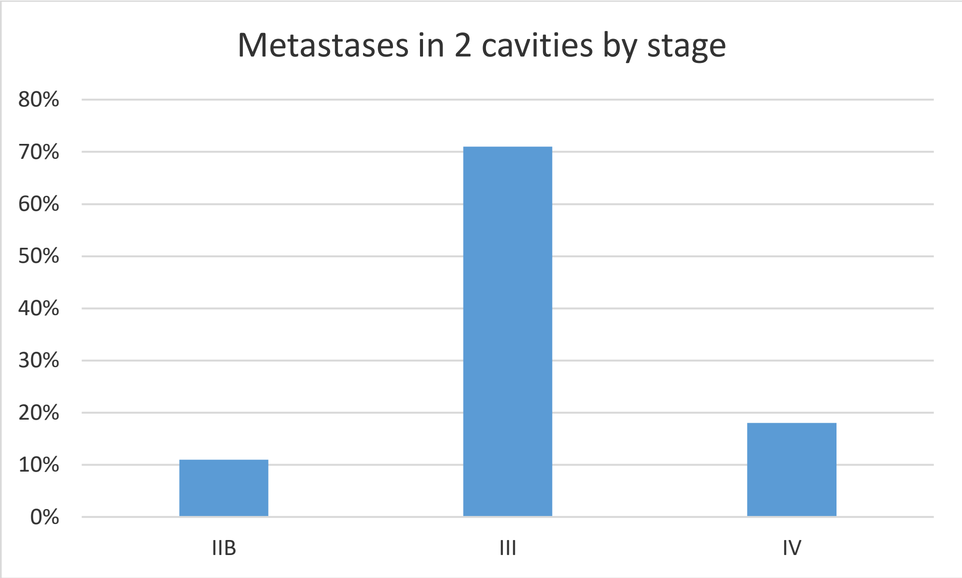


Fig. 49– Metastases in 2 cavities by stage

- 11% of the patients are in stage IIB - already with metastases in both cavities /16% have metastases in the regional lymph nodes, 11% in both cavities/.

11/16 - i.e. 0.69 or 69% of the operated patients in stage IIB with regional lymph node metastases already have spread metastases in both cavities.

- Even operable and extirpable, 11% of the patients in stage IIB have already metastases in both cavities, which proves the extreme aggressiveness of this tumour.

- 18% are patients with metastases in the celiac lymph nodes. It proves that the metastases in the celiac lymph nodes are a marker for systematic disease /these people were operated on because no metastases in the lymph nodes in this area have been proven preoperatively/.

Localization of the tumour with meta in two cavities in stage IIB

Siebert 1–	**1**
Siebert 2–	**1**
Siebert 3–	**0**
Distal third–	**1**
Middle third–	**3**
Cervical–	**0**

- At the earliest stage, compared to the other locations, carcinoma in the middle third of the oesophagus metastasizes in both cavities, which determines its most aggressive evolution. This fact is determined by the richness of the lymphatic drainage in this area.

T2–	**8**	**/ 18%/**
T3–	**33**	**/ 73%/**
T4–	**4**	**/ 9%/**

- The majority of patients are in stage T 3 - 73%.

- The low percentage of T4 stage is because most of these patients are inoperable due to distant metastases.

- 18% of the patients are in stage T2 - the tumour infiltrates through the submucosa, the submucosal lymph plexus and the muscularis and already in 18% metastasizes in both cavities before it has completely infiltrated the wall /22% are regional metastases, 18% are metastases in both cavities/.

18/22, i.e. 0.82 or 82% of those operated on in T2 stage, the metastases in the regional lymph nodes are already spread in both cavities - this fact shows how extremely fast is the malignant course and for how short time the metastases spread in both cavities.

By types of localization

Siebert 1–	**1**
Siebert 2–	**0**
Siebert 3–	**1**
Distal third–	**1**
Middle third–	**3**
Cervical–	**1**

CONCLUSION - AS IN STAGE IIB

By histology, of these 45 patients with metastases in both cavities

Adenocarcinoma	**21**	**/113 operated/**	**– 19%**	
Squamous cell	**21**	**/68 operated/**	**– 31%**	
Mixed	**2**	**/6 operated/**	**– 33%**	
Leiomyosarcoma	**1**	**/1 operated/**	**– 100%**	**/Fig. 50/**

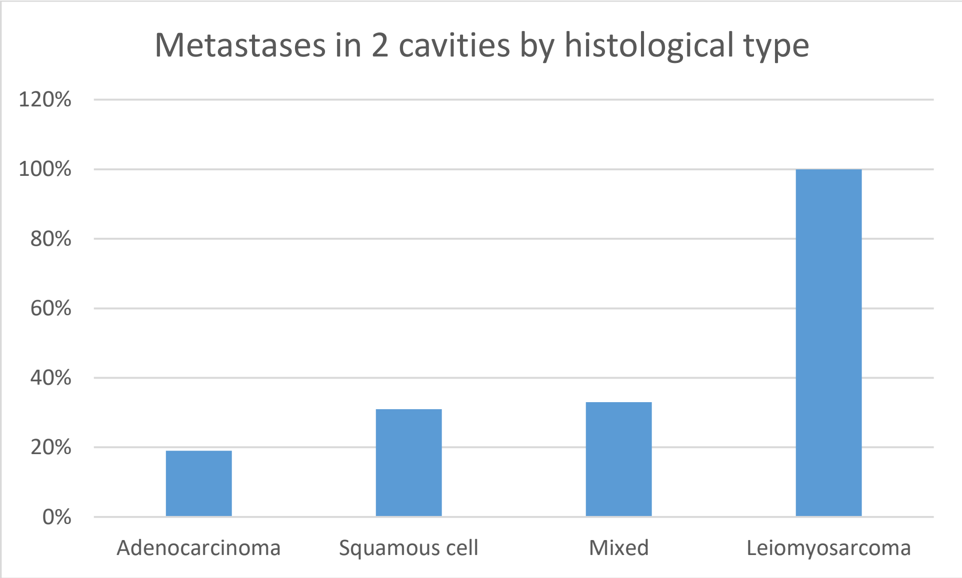


Fig. 50– Metastases in 2 cavities by histological type

Adenocarcinoma 21 /79 operated/ – 27%

Squamous cell 21 /41 operated/ – 51%

Mixed 2 /2 operated with metastases/ – 100%

Leiomyosarcoma 1 /1 operated/ – 100%

SQUAMOUS CELL CARCINOMA IS MORE AGGRESSIVE ABOUT DISTANT METASTASIS /IN TWO CAVITIES/, COMPARED TO ADENOCARCINOMA

28. Patients with "skipping" metastases

Total number of patients - 188

Patients with metastases - 123

Patients with "skipping" metastases - 34/28% OF THE PATIENTS WITH METASTASIS/

Siebert 1 – 6 /40 operated/ 15%

Siebert 2 – 7 /16 operated/ 44%

Siebert 3 – 6 /30 operated/ 20%

Distal third – 5 / 13 operated/ 38%

Middle third – 10 /22 operated/ 45%

Cervical – 0 /2 operated/ 0% /Fig. 51/

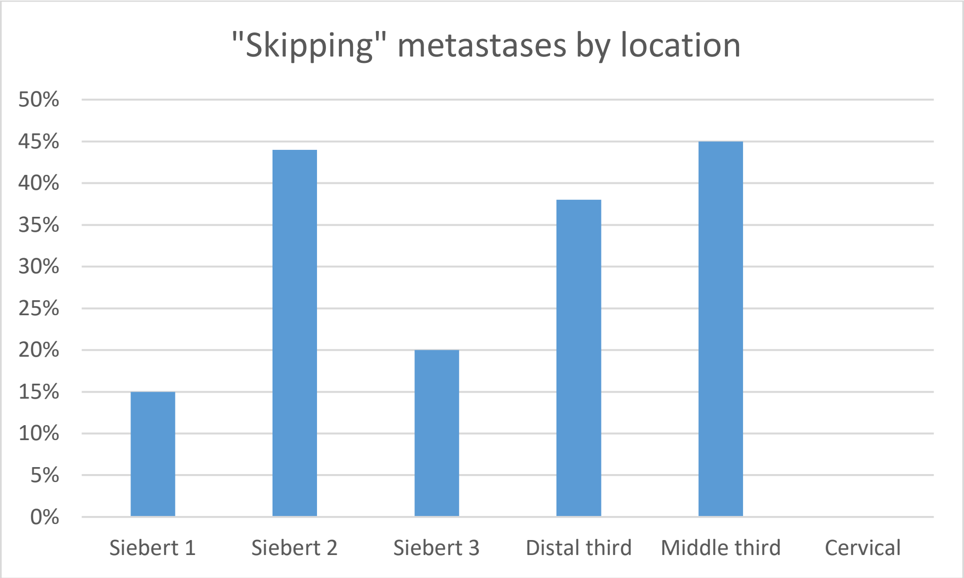


Fig. 51 - "Skipping" metastases by location

By histology, of these 31 patients with metastases in both cavities

Adenocarcinoma	**18**	**/113 operated/**	**– 16%**	
Squamous cell	**15**	**/68 operated/**	**– 22%**	
Leiomyosarcoma	**1**	**/1 operated/**	**– 100%**	**/Fig. 52/**

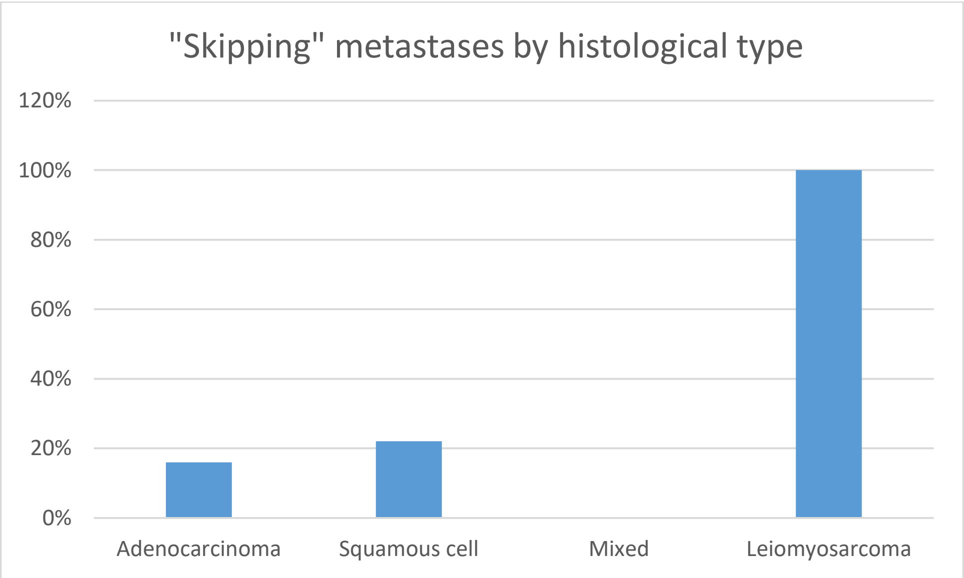


Fig. 52 - "Skipping" metastases by histological type

Adenocarcinoma	**18**	**/79 operated/**	**– 23%**
Squamous cell	**15**	**/41 operated/**	**– 37%**

Leiomyosarcoma 1 /1 operated/ – 100%

29. Patients without lymph node metastases in the regional lymph nodes

69 /188 operated/ – 37%

THE CANCER OF THE OESOPHAGUS IS AGGRESSIVE, QUICKLY METASTASIZING IN THE REGIONAL LYMPH NODES /63%/.

Of the patients without metastases in the regional lymph nodes, in 15/22%/ of them we find lymphatic vascular invasion, invasion in the arterioles and venules and perineural invasion.

Patients	Meta in the lymph vessels	Meta in the arterial and venous vessels	Perineural invasion
2010 N 0-9 N x -7	2 1	2 1	- -
2011 N 0-2 N x -2	- 1	- 1	- -
2012 N 0-8 N x -3	2 -	1 -	1 -
2013 N 0-9 N x -2	2 -	2 -	2 -
2014 N 0-17 N x -4	4 -	4 -	4 -
2015 N0-4 Nx-2	1 -	- -	1 -

Tab. 1 - Metastases in arterioles, venules and perineural invasion without lymph node metastases by age

Of these 15 patients in 13 we find lymphatic invasion

in 11 of them we observe an invasion in the arterioles and venules

in 8 of them there is a perineural invasion

T 1 – 0 /69 operated/ 0%

T 2 – 3 /69 operated/ 4 %

T 3 – 10 /69 operated/ 14%

T 4 – 2 /69 operated/ 3%

- None of the patients with T1 has tumour embolism /metastases/ in the regional lymph vessels, metastases in arterioles and venules, perineural invasion, but in stage T2 /where the muscularis is invaded/ it appears even before the metastases in the regional lymph nodes.

- In stage T2 there are already metastases in the regional lymph vessels, in the arterioles and venules, there is also a perineural invasion, but in 4% no metastases in the regional lymph nodes have appeared yet.

- At stage T3 this frequency increases to 14%.

- In T4, both operated patients had this type of metastasis.

Siebert 1 – 4	/60 operated/	7%	/operated NoNx 20 /	20%
Siebert 2 – 1	/26 operated/	4%	/operated NoNx 10 /	10%
Siebert 3 – 3	/38 operated/	8%	/operated NoNx 8 /	38%
Distal third – 3	/25 operated/	12%	/operated NoNx 11 /	27%
Middle third – 3	/33 operated/	9%	/operated NoNx 11 /	27%
Cervical – 1	/6 operated/	17%	/operated NoNx 4 /	25%

/Fig. 53/

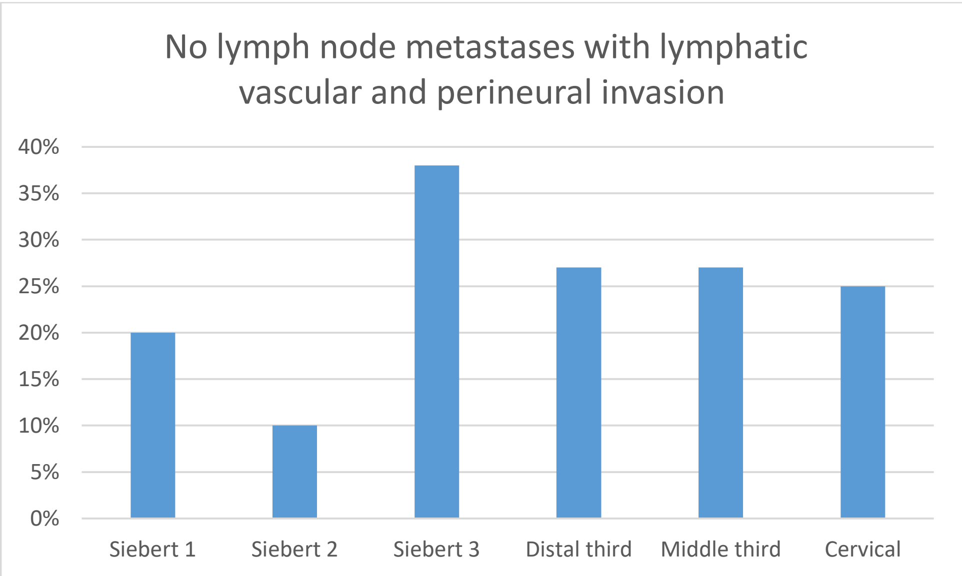


Fig. 53– No lymph node metastases with lymphatic vascular and perineural invasion

- Siebert 3 has the highest percentage without metastases in regional lymph nodes with invasion in regional lymph vessels, in arterioles and venules, perineural invasion.

Of these 15 patients without regional lymph node metastases, 13 had regional lymph vessel metastases, 11 had arteriole and venule metastases and 8 - perineural invasion.

- There is no preferred route of peritumoral invasion before the tumour has metastasized to regional lymph nodes.

Of these 15 patients:

Adenocarcinoma	**9**	**/113 operated/**	**– 7.9%**
Squamous cell	**6**	**/68 operated/**	**– 8.8%**

Table 2 - Comparison of metastases in different types of localization of oesophageal cancer

	Siebert 1	Siebert 2	Siebert 3	Lower third	Middle third	Cervical
Frequency	+++	++	++	++	++	+
Metastases in regional lymph nodes	++	++	+++	++	+++	+
Paratumor metastases	+++	++	+++	+	++	+
Metastases in the thoracic cavity	++	++	+	+++	+++	++
Abdominal metastases	++	++	+++	+++	+	++
Neck metastasis	+	-	-	-	+	+++
Number of metastases	++	++	+++	++	++	+
Metastases in 2 cavities	++	++	+	+++	++	+++
Metastases in 3 areas	+	-	-	-	+	+++
"Skipping" metastases	+	+++	+	++	+++	-
Early metastasis /stage IIB/	++	++	++	+	+++	+
Invasion of lymph vessels, arterioles, venules, perineural without meta in lymph nodes	++	+	+++	++	+++	++
Meta in cervical lymph nodes	+	-	-	-	+	+++
Meta in subaortic lymph nodes	+++	-	++	++	+	+
Meta in hilarious lymph nodes	-	-	-	+++	++	-
Meta in pulmonary ligament lymph nodes	+	+	+	-	++	-
Paraesophageal metastases	++	++	+	+++	+++	++
Cardia metastases	++	++	+++	++	+	+
Meta in small curvature lymph nodes	+	++	++	++	-	-
Meta in other lymph nodes - hepatic, lienal	++	-	+++	-	+	-
Celiac metastases	+++	+++	++	++	+	+

+ one or two metastatic nodes

++ three to five metastatic nodes

+++ over five metastatic nodes

- Oesophageal cancer is an aggressive malignancy.

- Although anatomically the predominant part of the oesophagus is located in the thoracic cavity, a higher percentage of metastases are found in the abdominal cavity.

- In the paratumoral, cardiac, paraesophageal and celiac lymph nodes, all localizations of the carcinoma are metastasized, which makes them mandatory in lymph dissection.

- There is a high percentage of metastasis in them /> 40%/. This is due to the aggressiveness of the tumour, which extremely rapidly metastasizes paratumorally and in the regional lymph nodes.

- A very small percentage of people have been operated only with paratumoral metastases /21%/, while the rest /79%/ have already had metastases in the regional lymph nodes. There is a large percentage of people, operated with metastases in both cavities /37%/ and patients with "skipping" metastases /28%/.

- Every third patient /37%/ has metastases in both cavities, which determines the aggressive malignant course of the tumour. Regardless of the localization, with the progress of the stage, metastases appear in two or three anatomical areas, which leads us to the conclusion that systematic lymph dissection is mandatory element of the treatment.

- The detection of even 2-3 metastatic lymph nodes /N 1/ sharply worsens the prognosis, because it can be on both sides of the diaphragm, which indicates the dissemination of the process.

- In the absence of metastases in the regional lymph nodes, the percentage of patients with invasion of lymph vessels, arterioles, venules and perineural invasion is high /22%/.

- The localization of the process does not determine postoperative mortality.

- In our series of patients, adenocarcinoma has an increasing frequency, as is the global trend /60%/. The last one and the squamous cell carcinoma have a similar rate of metastasis to regional lymph nodes, so it is not possible to determine which of them is more aggressive. In this series of patients, adenocarcinoma has twice as many paratumoral metastases, while the two types of carcinoma have a similar rate of regional lymph nodes metastasis. In this series of patients, squamous cell carcinoma has twice as many metastases in both cavities. The percentage of "skipping" metastases in squamous cell carcinoma is higher. In the absence of metastases /N o, N x/ the two tumours have a similar percentage of invasion in lymph vessels, arterioles, venules and perineural. Even more, the two types of tumours have a similar mortality rate in our series of patients.

- In the separated subaortic lymph nodes we find the highest percentage of metastatic ones, which defines this area of dissection as important. The tumour with the highest percentage of metastases here is Siebert 3, along with Siebert 1.

- Hilus and pulmonary ligament lymph nodes have a much lower percentage of metastases. The presence of metastases in them is a sign for a strong progression of the disease. By this characteristic, they are close to metastases in the celiac and cervical lymph nodes, on the condition that the cervical lymph nodes are regional for carcinoma of the cervical oesophagus and for the upper third of the oesophagus.

- Cardiac lymph nodes are most commonly affected by metastases in cases of oesophageal carcinoma, regardless of the location of the tumour. These nodes are the main route for the dissemination of the process.

- The lymphatic route involving the small curvature lymph nodes is not preferred, although we find metastases also here. In advanced stage of the disease, a high percentage of metastases is reported in the hilus of the spleen and liver.

- Given that the metastasis of the tumour in the celiac lymph nodes is a sign of distant metastasis, the high percentage in our series of patients determines the poor prognosis for them.

- Siebert 1 is the most commonly operated tumour in our series of patients. It metastasizes more often in the thoracic cavity and has a very high rate of paratumoral metastases. This is the tumour with the highest percentage of metastases in the subaortic lymph nodes, along with Siebert 3. From paratumoral metastases, the route of spread is in the paraesophageal lymph nodes. Some of the patients were operated on at this stage. After that, there are two ways of spread. One is toward the cardiac lymph nodes and there are no more metastases. The other is in the subaortic lymph nodes - this is the site of "skipping metastases". The third route is from the paratumoral lymph nodes directly to the cardiac lymph nodes, metastasizing there and then the route of metastases continues toward the celiac lymph nodes.

- Siebert 2 metastasizes more often in the abdominal cavity. There is a high percentage of "skipping" metastases. This is the tumour with the highest percentage of metastases in the celiac lymph nodes. The routes of spread are the same as in Siebert 1, but the more common route is toward the abdominal cavity - from paratumoral to paraesophageal or cardiac and then to celiac lymph nodes with a high percentage of "skipping" metastases.

- Siebert 3 has a very high rate of paratumoral metastases and metastases in regional lymph nodes. This is the tumour with the most metastatic lymph nodes removed by operated patient. Due to the fact that the stomach has a large lumen, carcinoma develops for a long time before it causes stenosis and respectively clinical manifestation, so this explains the large number of metastases. It metastasizes mainly in the abdominal cavity, very rarely in the chest cavity. This is the tumour with the highest percentage of metastases in the cardiac, but also in the lienal and hepatic lymph nodes. In the absence of metastases (No Nx), here we have the highest percentage of paratumoral invasion in the lymph vessels, arterioles and venules, as well as of perineural invasion. The routes of metastasis, as we noted, are mainly in the abdominal cavity. From the paratumoral lymph nodes, the metastases are directed toward the cardiac lymph nodes, where there are also metastases on the small curvature, as well as other metastases (lienal, hepatic). From there the metastases continue their route toward the celiac lymph nodes. As the process progresses, the route of metastasis is from the cardiac toward the paraesophageal and subaortic lymph nodes.

- Carcinoma of the lower third metastasizes evenly in both cavities. This tumour has the highest rate of metastasis in both cavities. It has the highest percentage of metastases in the hilar, paraesophageal and small curvature lymph nodes. Carcinoma of the lower third metastasizes in the paratumoral lymph nodes, the route then being predominantly toward the paraesophageal lymph nodes. In a smaller percentage of the cases, it metastasizes in the cardiac lymph nodes. From the paraesophageal lymph nodes, the routes in the thoracic cavity lead to the hilar lymph nodes in the pulmonary ligament. The routes in the abdominal cavity go from the cardiac to the small curvature and celiac lymph nodes.

- Carcinoma of the middle third has the longest duration of surgery as it poses serious technical difficulties. There is a very high rate of "skipping" metastasis in the regional lymph nodes. This tumour has the highest percentage of metastases at the earliest stage /II B/, which determines its fastest malignant course. It metastasizes mainly in the thoracic cavity. It has the highest rate of metastases in the pulmonary ligament. In the absence of metastases /No N /, here we have the highest percentage of paratumoral invasion in the lymph vessels, arterioles and venules, as well as of perineural invasion. Carcinoma of the middle third mainly metastasizes in the paratumoral lymph nodes and then in the paraesophageal lymph nodes. The routes are toward the lymph nodes in the thoracic cavity (hilus, pulmonary ligament), but there are also metastases in the neck area. A smaller proportion of metastases is directed to the cardiac and celiac lymph nodes.

- Carcinoma of the cervical esophagus is characterised by metastases in all three areas of lymphatic dissection with the highest percentage of metastases in the cervical area. This carcinoma creates paratumoral metastases in the cervical lymph nodes, which are subsequently detected in both the thoracic and abdominal cavities.

5. BEHAVIORAL SELECTION ALGORITHM

LYMPH DISSECTION

- We perform dissection of lymph pools in 2 anatomical areas by groups - in the chest and in the abdominal cavity.

- We send lymph nodes for express histological examination, because the prognosis is different even with a positive metastatic lymph node. In this way the stage and, accordingly, the survival change.

- We have already checked the distant lymph nodes for "skip" metastases.

- The volume of the lymph dissection is determined by the local finding and in the presence of N 1 local lymph nodes we always do maximally expanded lymph dissection in two areas.

- In cardiac carcinoma and in the absence of local metastatic lymph nodes, the patient falls into stage II A - we do lymph dissection on N 1 and N 2 groups of lymph nodes.

- The other patients fall into stage II B - we do maximally expanded lymph dissection in 2 anatomical areas /chest and abdominal cavity/. Lymphatic dissection of the neck is not performed in cardiac cancer.

- We do cervical lymph dissection only if we have palpation and computed tomography data for enlarged cervical lymph nodes.

- We monitored patients at 1 month, 3 months, 6 months, 1 year after surgery. All patients were referred to an oncologist for chemotherapy. Patients are not subject to radiation therapy.

OPERATIVE INTERVENTION

- One-stage operation /resection with reconstruction/

- Maximum radicalism /up to subtotal resection of the oesophagus with extended lymphatic dissection/ - the aim of the operation is to reach the maximum radicality of the intervention /R 0/. Proximal and distal 10 cm /8-12 cm/ of oesophageal carcinoma, measured on the patient in the operating theatre is enough to achieve R0 resection /keep in mind that the automatic suture also takes 1-2 cm from the tissues of the organs involved in the future anastomosis. It is estimated that micrometastases are detected at such a distance in a maximum of 3% of the patients

- Lymphatic dissection /> 15 lymph nodes/ - we count the lymph nodes separated around the oesophageal-gastric resectate *en bloc*.

- The stomach is the most suitable choice for reconstruction /the cardia and the small curvature are cut/ - the advantages include easy construction and perspective for achieving sufficient length. A wide (at least 5 cm) stomach tube is used. The use of a full stomach is less common. The colon is used in patients who have had previous gastric surgery or other procedures that have resulted in gastric devascularization.

- The posterior mediastinum is the way to interpose the graft - it is placed in a posterior-mediastinal /orthotopic/ position - this is the shortest, most direct and most functional route. This procedure cannot be used in case of a tumour infiltration or inflammatory changes in the mediastinum.

- Left Transthoracic Transdiaphragmatic Access (LTTA) with resection of the oesophagus and stomach with subsequent intrathoracic Gastro-Oesophago Plastic Stent (GEPS) placement is used for carcinoma of the cardia and lower third of the oesophagus.

- Avoiding severe operative trauma and unnecessary risk of the intervention, we do not apply cervical lymph dissection in operated patients with LTTA.

- Resection and plastic surgery of the oesophagus with the stomach by left thoracotomy and phrenotomy showed the following advantages over other techniques:

- Shorter operating time
- Precise lymph dissection in two fields with less blood loss
- Reduced postoperative complications

6. CONCLUSIONS

For the complex assessment of lymphatic dissection in oesophageal carcinoma, we consider important:

- Evaluate the possibility of lymph dissection in 2 or 3 areas in different types of surgery /Laparotomy, Right thoracotomy, Left thoracotomy and Cervicotomy /;

- Surgical intervention is tailored to the stage, location and type of tumour;

- Clarification of the dissection by anatomical areas;

- Intraoperative stage assessment through express histological diagnosis;

- Assessment of the frequency of "skipping metastases" and determination of "lymph node ratio";

- Application of a scheme for precise mapping of lymph nodes;

- Creating an algorithm for lymph dissection according to the stage and location of the tumour;

- Left thoracotomy with phrenotomy has the advantage of complete dissection in two areas /thoracic and abdominal/.

PRACTICAL CONCLUSIONS FOR THE LYMPH-VASCULAR INVASION / LVI /

1. LVI is proven in all cases with lymphogenic metastases.

2. Applying histochemical and immunohistochemical studies, LVI is found in 75% of the studied cases in N0, mainly in pT2 and pT3, and may complement the characteristics of the tumour evolution and be the only risk factor with prognostic value in stage N0.

3. IHC examination of the tumour and its microenvironment, as well as of the lymph nodes with perinodal adipose tissue, is a recommended method for detecting tumour embolism when the interpretation is difficult with routine morphological examination.

4. We confirm the observation that LVI increases in stages pT2 and pT3 of the tumour, due to the increased volume of its mass, the increase of the growth fraction and the accumulation of various gene mutations, some of which are associated with the potential for local invasion and metastasis

5. The frequency of LVI and lymphogenic metastases does not depend on the location of the tumours in the distal oesophagus or in the oesophageal-gastric junction.

7. SUMMARY

1. In TNM staging, UICC prognostic factors are: the depth of tumour invasion (T), the presence or absence of lymph node involvement (N), the presence or absence of more distant metastases (M) and the category of radical intervention with the conditions of the resection lines /R/.

2. Lymphatic vascular invasion (LVI) is a strong and independent prognostic factor in squamous cell carcinoma of the oesophagus and adenocarcinoma of the stomach. Its association with distal oesophageal adenocarcinoma and cardiac carcinoma has not been established.

3. LVI has not been accepted as a factor in the oesophageal carcinoma staging

4. The inclusion of LVI is an essential sign, noting the onset of aggressive carcinoma behaviour.

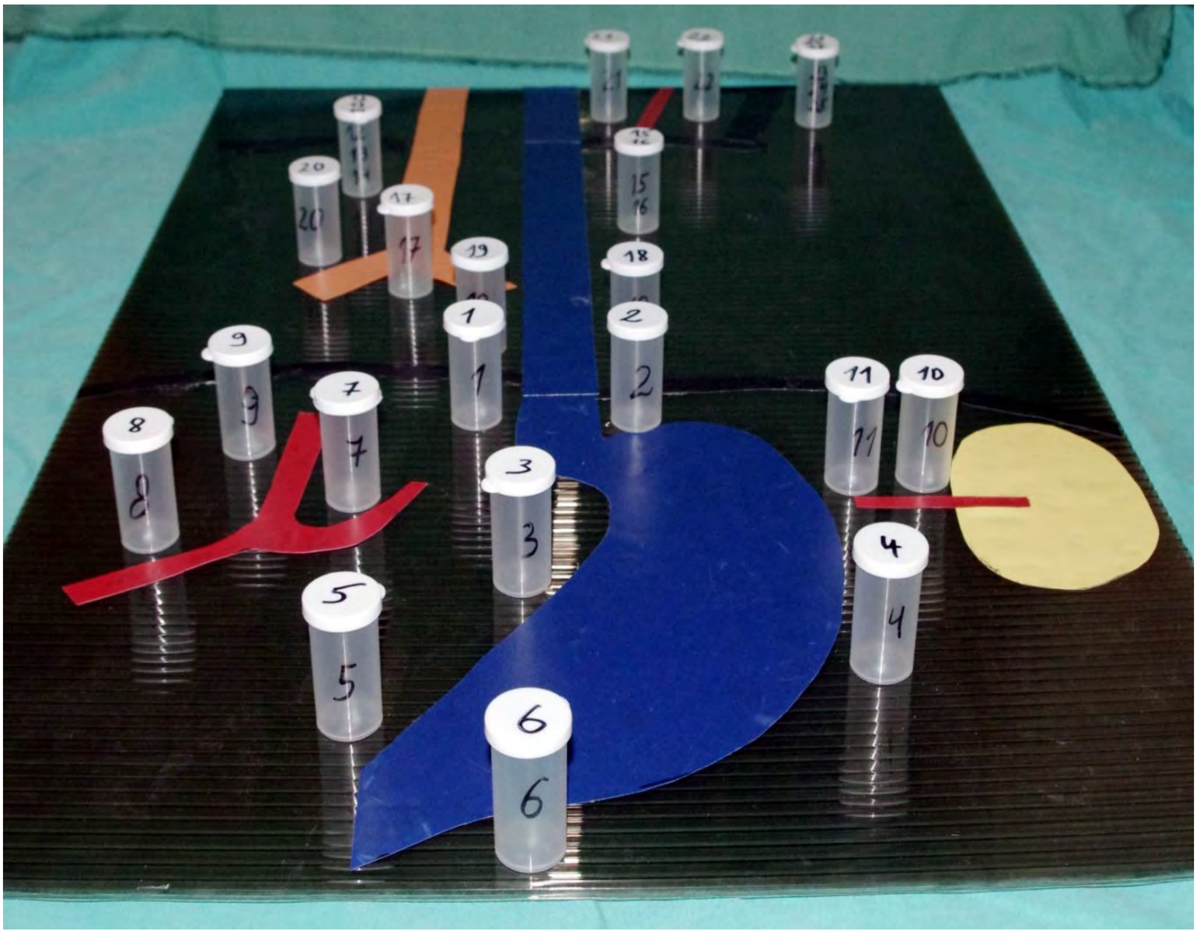
5. Of undeniable interest in this regard is to clarify the role of the vascular invasion, which precedes lymphogenic metastases.

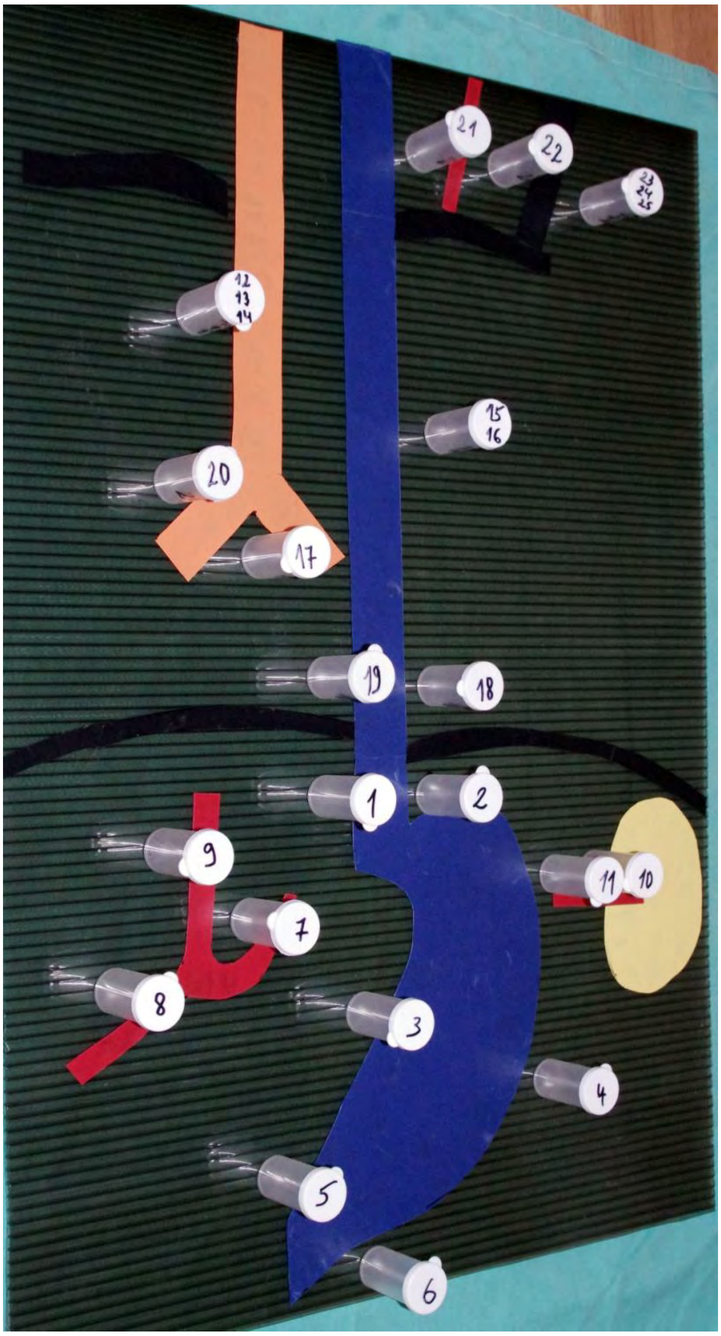
6. Lymphatic invasion is considered to precede or occur simultaneously with lymph node metastases.

7. Patients with early carcinoma (T1) and carcinoma without involvement of nodular metastases (N0), show a significant amount of lymph vessel invasion. This is due to the aggressiveness of these tumours.

8. Lymphatic invasion is associated with more advanced stage of the disease, as patients with more advanced tumours have a higher incidence of lymphatic vascular invasion.

8. <u>LYMPH NODE MAPPING TRAY</u>





Photos 8, 9 of the lymph node tray - bottom view and oblique view

9. CONTRIBUTIONS

1. We propose a new application for assessment of lymphatic metastasis with lymphatic dissection of oesophageal carcinoma based on the combination of two internationally accepted classifications /the Japanese for the abdomen and Mountain and Dressler's for the chest/.

2. We apply a precise scheme for mapping the lymph nodes.

3. We offer a broader approach to D1, D2, D3 lymph dissection - so far D1-dissection in one area, D2-dissection in two areas, D3-dissection in three areas, considering that there may be D1 D2 D3 dissection in three areas as it is by the Japanese classification.

4. Technical description of the surgical intervention for the new D1 D2 D3 dissection.

5. Indications and methods of performing D1, D2, D3 lymph dissection have been developed.

6. We suggest the possibility to study the lymphatic vascular invasion in order to determine adjuvant therapy and the prognosis of oesophageal carcinoma.

10. PUBLICATIONS AND PRELIMINARY REPORTS, RELATED TO THE DISSERTATION

1. Choice of operative access for cardiac cancer - D. Vrachanski, T. Atanasov, St. Sopotenski, J. Tsenovski, A. Filipov, P.A. Chervenyakov, Al. Chervenyakov - XIV National Congress of Surgery 2014 - Sofia

2. Evaluation of lymph dissection and surgical staging with view of radical surgery for adenocarcinoma in the lower third of the oesophagus and cardia - J. Tsenovski, S. Sopotenski, D. Vrachanski, T. Djendov, B. Borisov, A. Chervenyakov - Sixth National Congress of thoracic, cardiac and vascular surgery 2015 - Sandanski

3. Unified classification in carcinoma of the oesophagus and cardia based on lymphatic metastasis - J. Tsenovski, A. Chervenyakov - Journal of Surgery Vol 81 / 3.2015, pp. 123-134

4. Cardiac carcinoma - J. Tsenovski, A. Chervenyakov - Medical magazine, issue 22 / month 10.2015, pp. 78-83

5. Evaluation of the lymphatic distribution and the volume of lymph dissection in view of the radical surgical intervention in cardiac carcinoma - J. Tsenovski, S. Sopotenski, D. Vrachanski, T. Djendov, B. Borisov, A. Chervenyakov - Bulgarian journal for thoracic, cardiovascular and vascular Surgery - Issue 2, 2015 (№ 2, 2015) - pp. 13-21

6. Oesophageal carcinoma - J. Tsenovski, A. Chervenyakov - Medical magazine, issue 30 / month 06.2016, pp. 74-79

7. The role of lymphatic-vascular invasion in the prognosis of oesophageal carcinoma - J. Tsenovski, M. Kamenova, O. Bogdanova, S. Sopotenski, A. Chervenyakov - XV National Congress of Surgery - Albena 2016

8. Squamous cell or adenocarcinoma of the oesophagus - the various carcinomas - J. Tsenovski, S. Sopotenski, A. Chervenyakov - XV National Congress of Surgery - Albena 2016.

9. The role of lymphatic-vascular invasion in the prognosis of oesophageal carcinoma - J. Tsenovski, M. Kamenova, O. Bogdanova, S. Sopotenski, A. Chervenyakov - Sixth National Congress of Thoracic, Cardiac and Vascular Surgery 2017 - Pravets

10. Surgical treatment of squamous cell and adenocarcinoma of the oesophagus - D. Vrachanski, S. Sopotenski, J. Tsenovski, B. Borisov, A. Chervenyakov - XVI National Congress of Surgery - summer resort Golden Sands - Varna

11. Postoperative complications in lymph dissection in oesophageal surgery for cancer - D. Vrachanski, S. Sopotenski, J. Tsenovski, D. Korunoski, M. Mladenov, A. Chervenyakov - XVI National Congress of Surgery - summer resort "Golden Sands" - Varna 2018 - Poster

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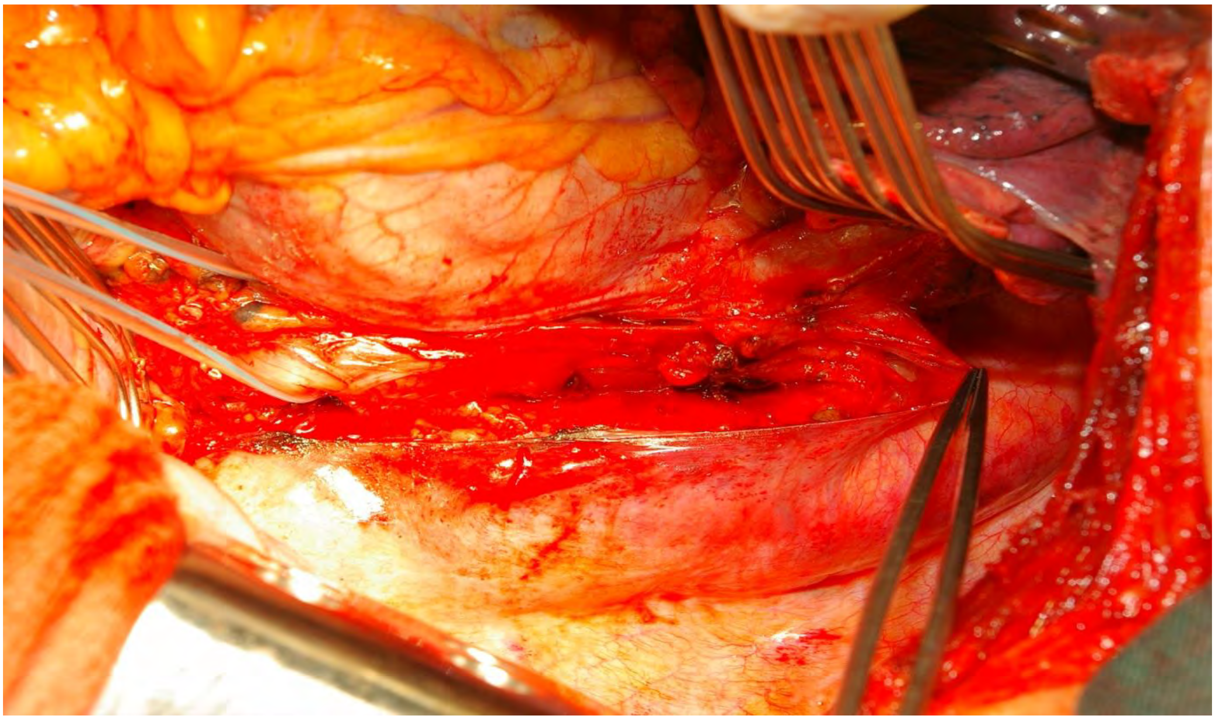
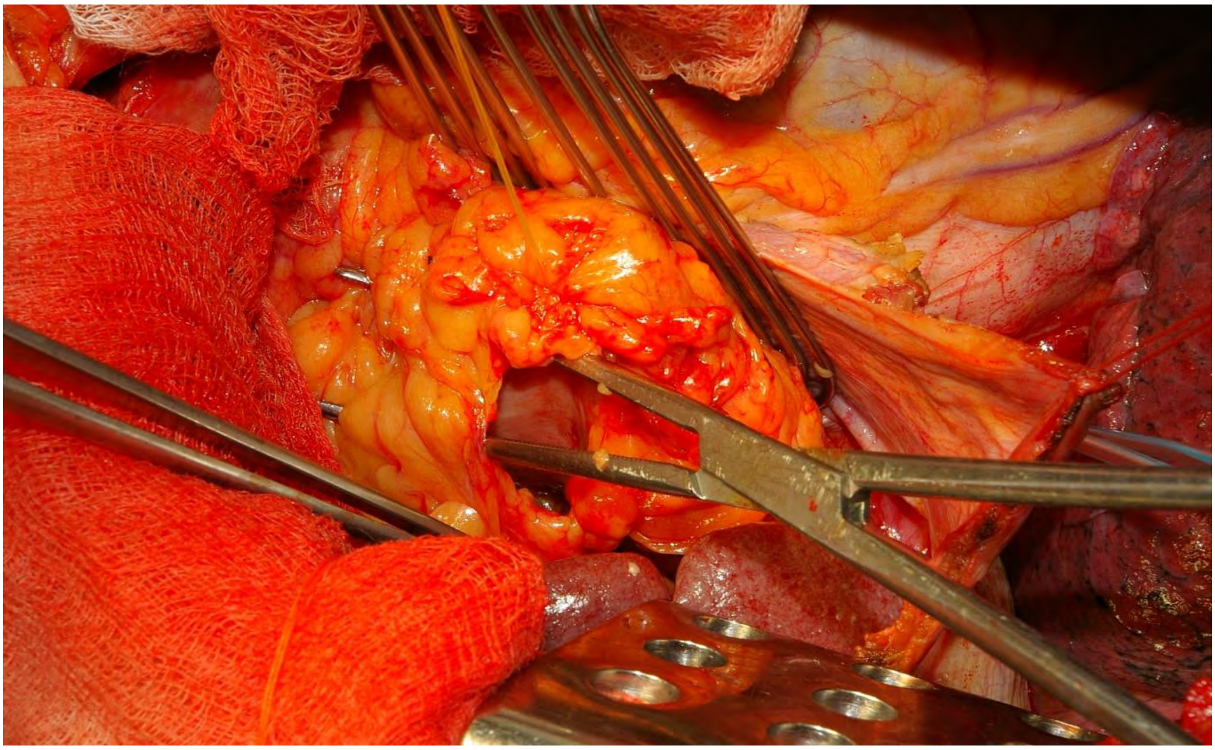
12. APPENDIX

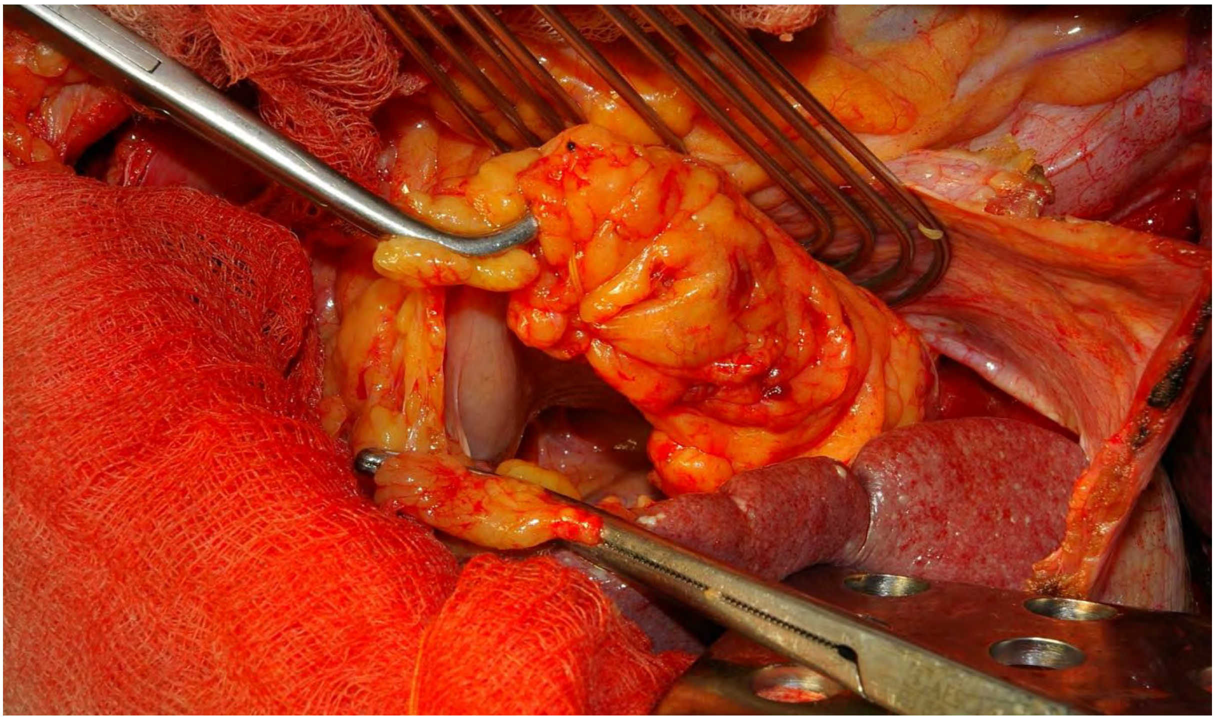
Appendix 1 - RELEASE OF THE PULMONARY LIGAMENT WITH LYMPH DISSECTION AND INSTALLATION OF THE ESOPHAGUS ON A STAND



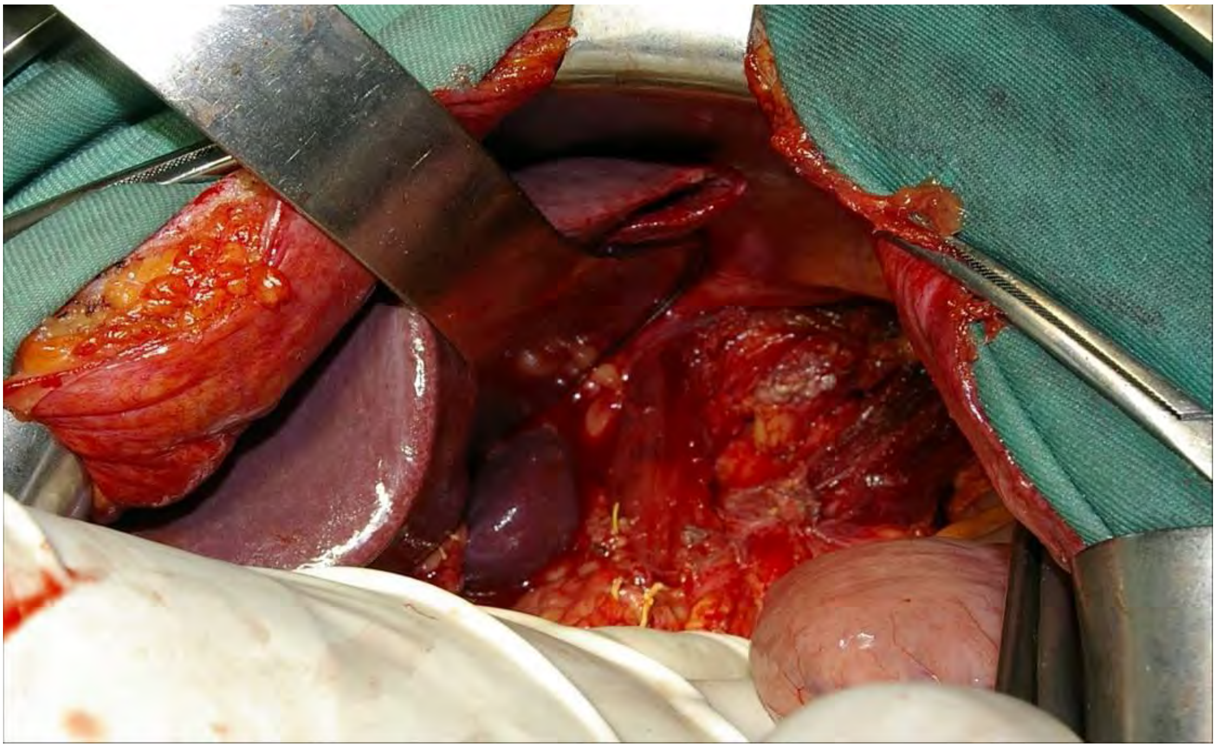
Appendix 2 - PREPARATION OF THE OESOPHAGUS FROM THE DIAPHRAGM TO THE AORTIC ARCH WITH INTRATHORACIC LYMPHATIC DISSECTION /LIGAMENTUM PULMONARY, PARAESOPHAGEAL, HILAR, SUBCARINAL, PARATRACHEAL LYMPH NODES/



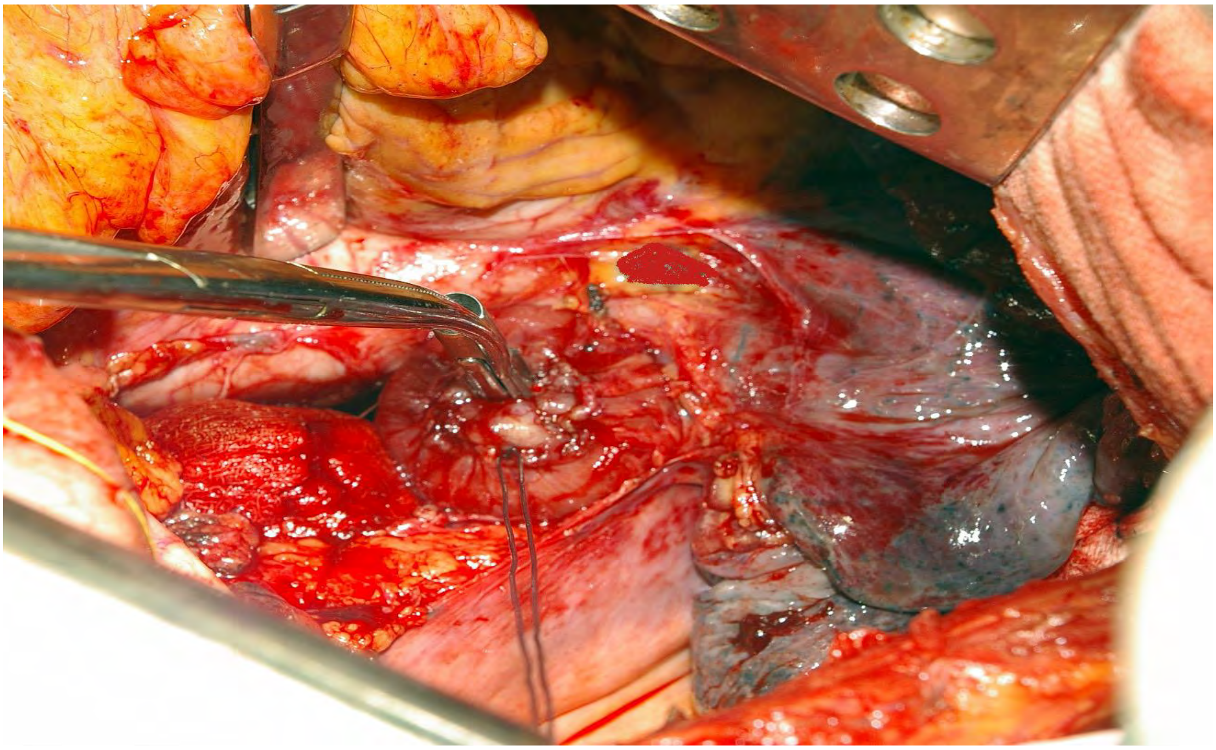
Appendix 3 - OPENING OF THE DIAPHRAGM AND SKELETONIZATION OF THE STOMACH WITH LYMPH DISSECTION PARACARDIALLY - SUPERFICIALLY - ACCESSIBLE ABDOMINAL LYMPH NODES - /STOMACH-TRANSVERSAL, STOMACH--LINEAR, STOMACH, DIAPHRAGMATIC, OESOPHAGO-DIAPHRAGMATIC, OESOPHAGO-GASTRIC, HEPATO-DUODENAL CONNECTION/



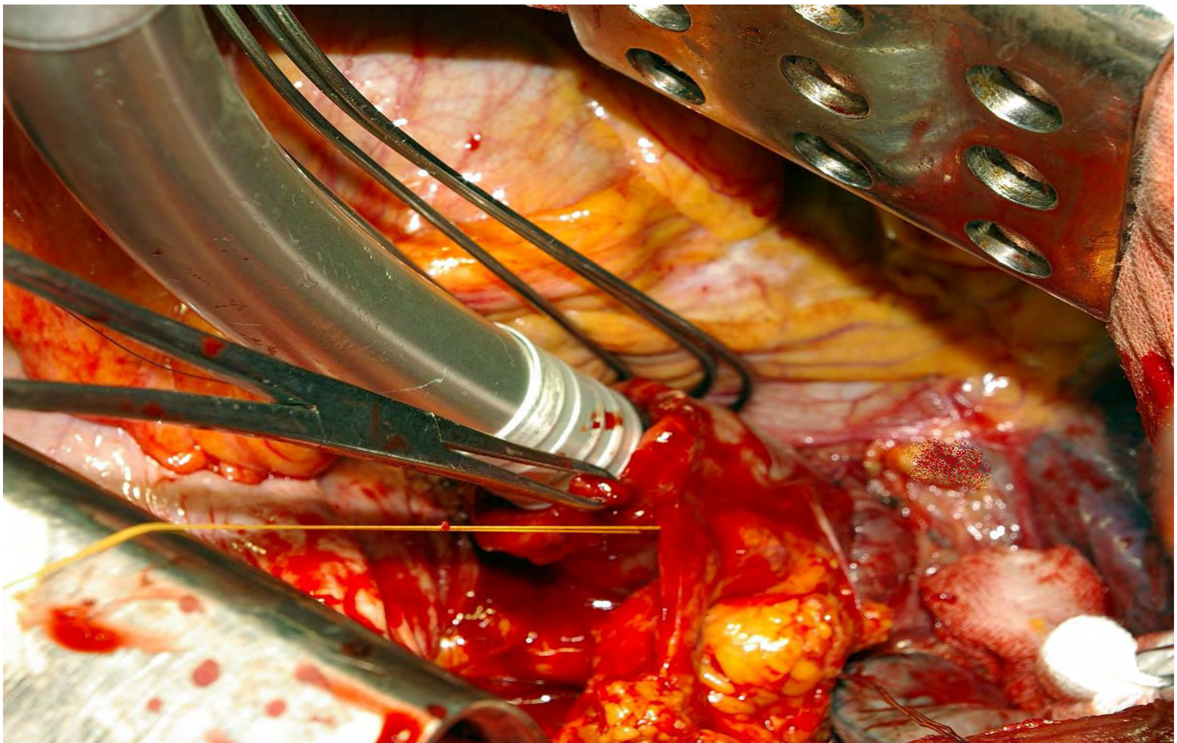
Appendix 4 - RELEASE OF THE STOMACH ON THE GREAT CURVE WITH ACCESS TO A. GASTRICA SIN.



Appendix 5 - ACCESS, INSPECTION AND LYMPH DISSECTION TO TRUNCUS CELIACUS AND PARAAORTALLY /AVAILABLE ABDOMINAL LYMPHS NODES - VISCERAL / CELIAC., A. GASTR. SIN., A GASTR. DEX., LIENAL AA., HEPATIC A., PANCREATODUODENAL, PARAAORTALLY/

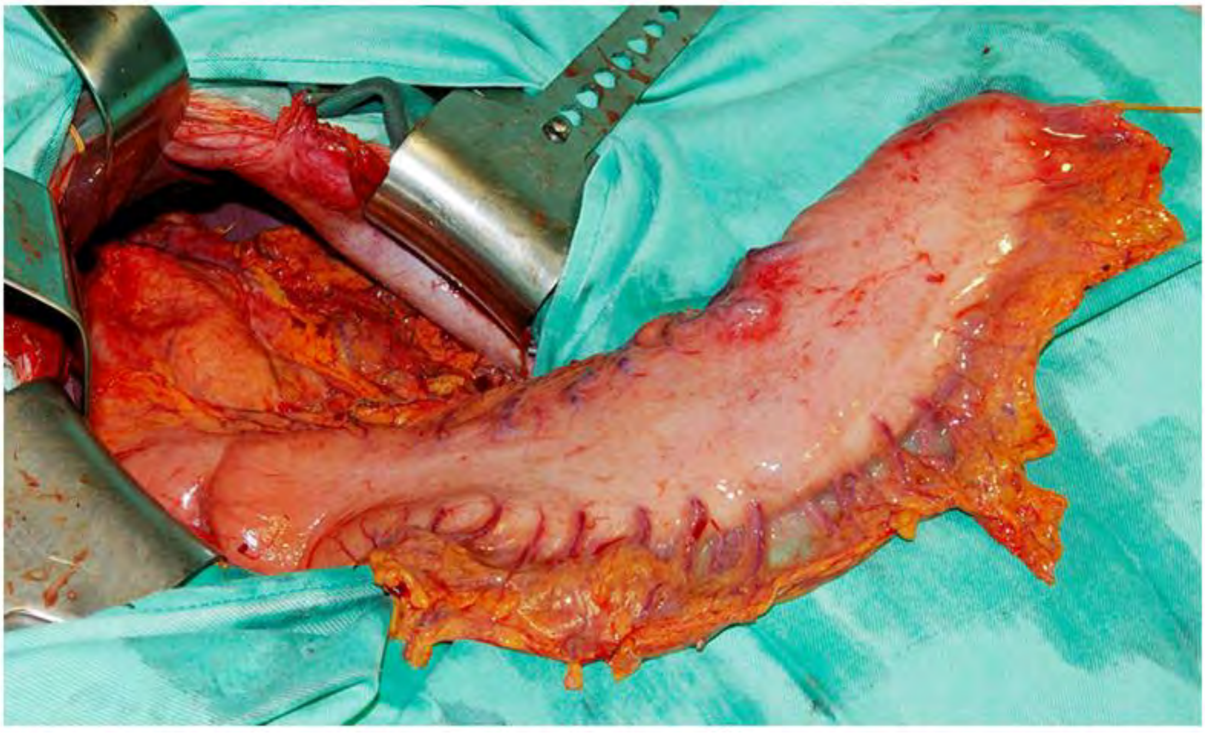


Appendix 6 - FIXING THE STAPLE HEAD AND TIGHTENING THE PURSE-STRING SUTURE

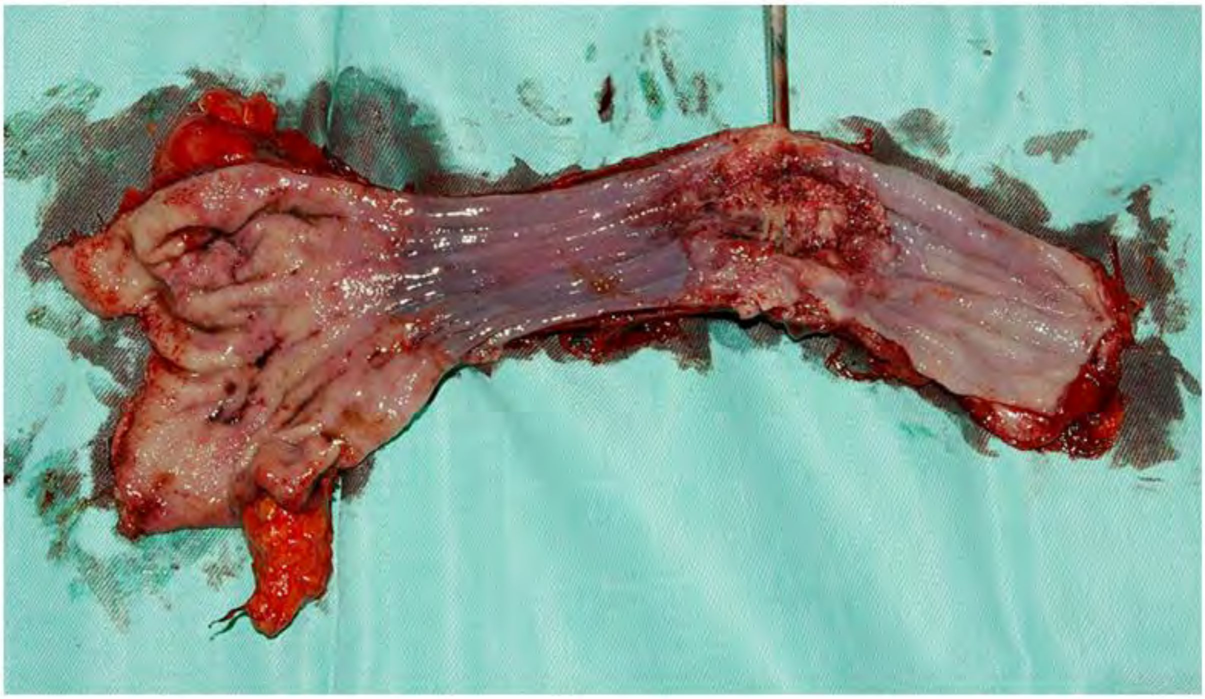


Appendix 7 - CREATION OF AN ANASTOMOSIS WITH AN AUTOMATIC PURSE-STRING SUTURE

Appendix 8 - CERVICAL ESOPHAGO-GASTRO ANASTOMOSIS WITH SINGLE SUTURES WITH CERVICAL LYMPH DISSECTION /PRESCALENE LYMPH NODES, SUPRACLAVICULAR LYMPH NODES, DEEP AND SUPERFICIAL CERVICAL LYMPH NODES, SUBMANDIBULAR LYMPH NODES/



Appendix 9 - VIEW OF GASTRO-OESOPHAGEAL GRAFT



Appendix 10 - SQUAMOUS CELL CARCINOMA IN THE MIDDLE THIRD OF THE OESOPHAGUS

Appendix 11 - PLAN VIEW OF THE PREPARATION WITH RIGHT-SIDED TRANSTORACAL ACCESS AND LAPAROTOMY (DTDL) - CARDIAL ADENOCARCINOMA TYPE SIEBERT III, T3, N1, M1