The role of the neoadjuvant therapy in the surgical treatment of localy advanced oesophageal cancer

PhD Thesis
(Summary)

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I. Introduction

After an article about epidemiology of GI cancers published in 2003, oesophageal cancer represents 5.9% of all GI cancers in Europe. Oesophageal cancer mostly occurs in the elderly - between 60 and 80 years - with a 3:1 male-female ratio. It was also published there, that 829 new esophageal cancer cases occured in Hungary in 2002, whereas the number of deaths were 709. Against the data from the USA and Western Europe, squamous cell oesophageal cancer remained the dominant type in Hungary, which has a worse prognosis compared to adenocarcinoma cases. Surgical resection offers the only curative approach, although at the time of the diagnosis nearly one third of the patients are not feasible for any curative treatment. The poor prognosis may further be worsened by the difficulties arising from tumor location. Namely, it is more difficult to perform an adequate lymphadenectomy in case of an upper-third located tumor compared to a lower-third one (below the level of the azygos vein), at the cost of a higher complication rate. This seems to be a feasible explanation for the worse prognosis of the the proximaly located disease. It seems clear now, that the development of the surgical technique alone can not improve this poor prognosis.

According to these above mentioned facts, we have searched the answers to the treatment problems of localy advanced cancer located in the upper part of the oesophagus in this work.

II. The role of the neoadjuvant therapy in the surgical treatment of localy advanced oesophageal cancer

II.1 Introduction

Due to the poor surgical results, different combinations of surgical, radio and chemotherapy are under research, to improve the prognosis. The combination of chemo- and radiotherapy has superior effect over radiotherapy alone in the treatment of oesophageal cancer in an advanced stage. The great advantage of combined preoperative treatment over the adjuvant therapy is that in neoadjuvant therapy the two different treatment modalities synergicly increase each others effects on cancer in an environment with unharmed lymphatic circulation and blood supply. Neoadjuvant therapy is able to induce downsizing of the primary lesion, decreases the potential for metastases, increases the resectability rate and consequently improves long term survival. Not detailing the different trends of the oncological treatment, the current routinely used protocols incorporate irradiation (35-45 Gy dose) and synchronously given chemotherapy (platine derivate combined with 5-FU).

II.2. Patients and methods:

In the Department of Surgery, Medical Faculty, University of Pécs 382 oesophageal resections were performed due to cancer between Jun. 1992 and Sept. 2005. (cardiac tumors were excluded) However, according to the data that neoadjuvant therapy has favorable effect in the treatment of oesophageal cancer, patients with locally advanced (T3,T4,Nx) squamous cell carcinoma located at or above the tracheal bifurcation were selected for multimodal therapy from Nov.1997.

In this retrolective study, any patient who had histologically proven locally advanced oesophageal squamous cell cancer without distant metastases and was considered medically fit for surgery (age<75 years, Karnoffsky score>60%) was eligible, if the tumor was located at or above the tracheal bifurcation. Patients with previous chemo- or radiotherapy in the medical history were excluded. Informed consent was obtained from all patients. In all patients the staging procedures included endoscopy, endoscopic ultrasound, barium swallow, chest X-ray, abdominal and cervical ultrasound, computed tomography (CT) scan and bronchoscopy with brush cytology or biopsy. Between Nov.1997 and Sept. 2005 102 patients were enrolled. The mean age was 55.5 years, regarding sex ratio a high male dominance was observed. (90 males:12 females) Following the staging, patients received concomitant chemo-radiotherapy, with the external beam irradiation (CT based three-dimensional conformal radiation method was used). **(Table I.)**

Table I: Treatment protocol

- *1st. day:* radiotherapy + Cisplatin (75 mg/m^2) infusion
- *1st-5th day:* radiotherapy + 5 FU 1000mg/m^2 with Ca-folinate 20 mg/m^2 infusion
- *From 8th day onwards:* radiotherapy alone

Radiotherapy: 180 cGy external beam once daily for 5 days weekly (up to 3960 cGy)

After a four-week-long treatment free period restaging was carried out and patients considered resectable were submitted to surgery. As a first step, to prove the efficiency of the preoperative chemo-radiotherapy the neoadjuvant group was compared to a historical control group of 65 patients, who were operated on between Jun. 1992 and Nov.1997 with locally advanced squamous cell oesophageal cancer located at or above the tracheal bifurcation. There was no statistically significant difference between the patient groups regarding age, gender, etc. **(Table II.)**

Table II: Clinical data

Historical control group 1992 Jun. - 1997 Nov. 65 patients (T3-T4)

- T3/T4: 39/26
- Resection: 65 R0 resection: 49/65 (75%)
- Female/male: 6/59
- Mean age: 56,15 years (36-72)

CRT+Surgery Group 1997 Nov. - 2005. Sep. 102 patients (T3-T4)

- T3/T4: 45/57
- Resection: 71, R0 resection: 59/71 (83%)
- Female/male: 12/90
- Mean age: 55.55 years (41-73)

Group 1 40 patients
- T3/ T4: 21/19
- Resection: 28/40
- Female/male: 5/35 male
- Mean age: 54 years (41-70)

Group 2 62 patients
- T3/T4: 24/38
- Resection:43/62
- Female/ male: 7/55
- Mean age: 57.11 years (41-73)

To evaluate the response, the complete staging procedure detailed above was repeated and then the following classification was used:
Complete remission: significant downsizing of the disease (normal oesophagogram, endoscopy and CT scan) and no viable tumor cell in the histological sample of the resected specimen.
Partial remission: viable tumor cells in the histological evaluation, but the downsizing of the tumor was greater than 50%.
Stable disease: tumor regression was less than 50%.
Progression: tumor size increased, fistula formation or distant metastasis appeared.

II.3 Results:

During restaging a clear downsizing of the primary lesion was visible. **(Figure 1.)**

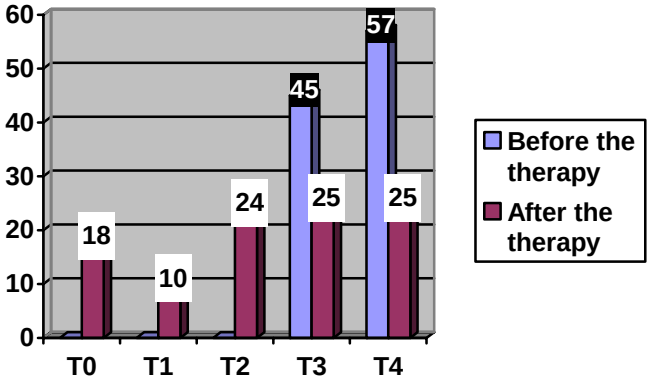


Figure 1: Downsizing of the primary lesion

After the neoadjuvant treatment 82 from the 102 cases were eligible for surgery, however in 11 cases only exploration was accopmplished, thus the resection rate was 71/82 (86,6%). In 59 patients R0 resection was performed (83%). The histopathological examination of the resected specimens confirmed pathological complete remission (pCR) in 17 patients (24%). In the postoperative period the mortality rate was 16.9% (12/71), and the postoperative morbidity rate was 55% (39/71) Anastomotic leakage occured in 11 patients (15.5%) and pulmonary complications in 20 patients (28.2%). **(Table III.)**

Table III.: Treatment results

RESPONSE		
Complete remission:	17/102	(16,7%)
Partial remission:	54/102	(52,9%)
Stable disease:	16/102	(15,7%)
Progression:	15/102	(14,7%)
TREATMENT RESULTS		
Surgery:	82/102	(80,4%)
Exploration:	11/82	(13,4%)
Resection:	71/82	(86,5%)
R0 Resection:	59/71	(83,1%)
COMPLICATIONS		
Perioperative mortality	12/71	(16,9%)
Perioperative morbidity	39/71	(55%)
Anastomosis leakage	11/71	(15,5%)
Pulmonary complications	20/71	(28,2%)
Other	8/71	(11,3%)
In Hospital stay (days)	17.54 (9-54)	

During the survival analysis, the multimodal therapy group was compared to a historical control group first, where surgery was done alone. Mean survival after the neoadjuvant CRT combined with surgery was significantly better compared to the surgery alone group. (22.7 months vs 9.3 months p:0.001) **(Figure 2.)**

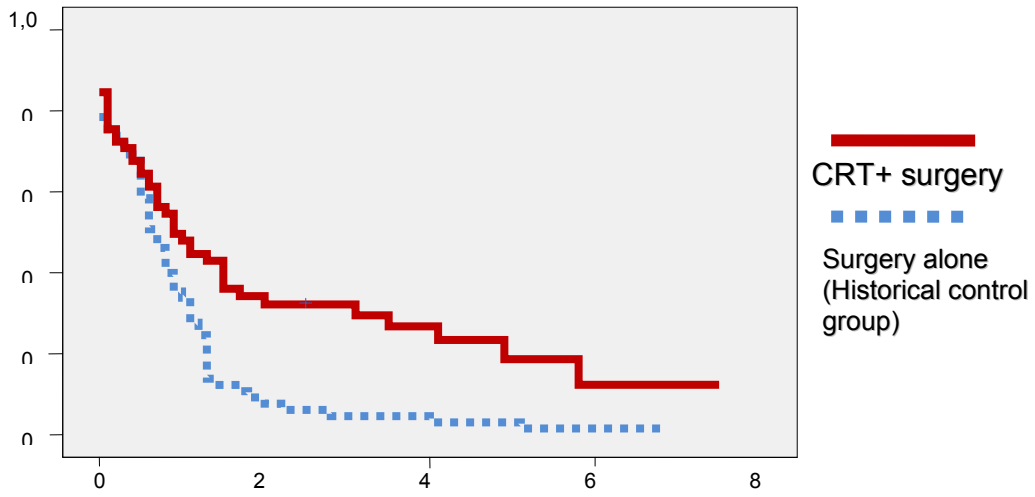


Figure 2.: Survival analysis: CRT resulted in significantly better mean survival

The mean survival of cases with complete remission was significantly longer compared to the other cases. (33 months vs 13.3 months, p:0.024) **(Figure 3)**

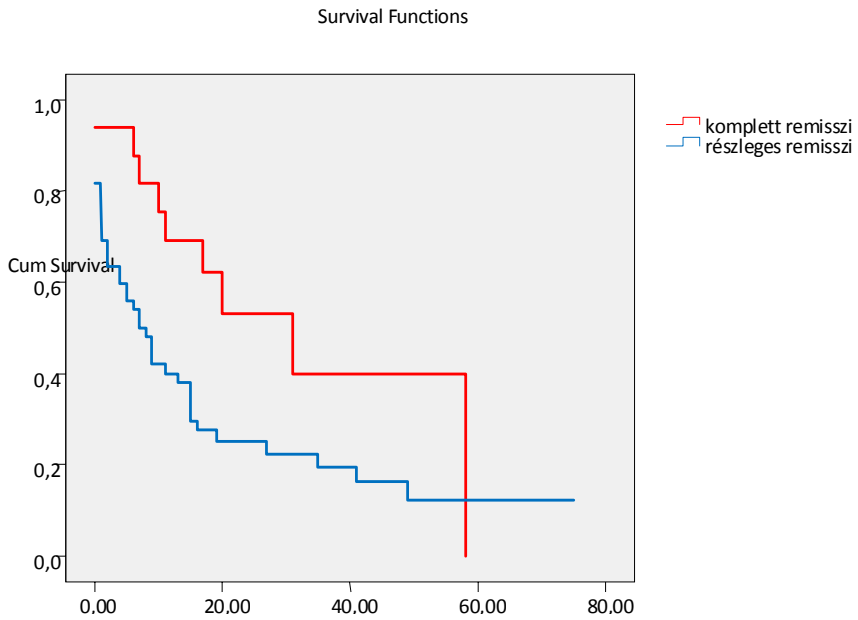


Figure 3: pCR means significantly longer survival

II.4 Discussion

The preoperative chemo-radiotherapy in Hungary was firstly intrudoced by us in the treatment of locally advanced oesophageal cancer. With the help of this new, multimodal treatment previously irresectable cancer cases could be resected with curative intention. According to the literature we also proved, that the preoperatively applied chemo-radiotherapy improved the long term survival rate in locally advanced squamous cell oesophageal cancer. It was also proven, that patients with pathological complete response (pCR) had significantly better survival compared to all the others, and that the pCR is an independent prognostic factor. Based on these results we believe that the surgical resection is currently the only method to document the complete response to neoadjuvant therapy. In case of pCR surgical treatment can still be advised, thus the group with the best survival

chance will receive the highest level of local tumor control. Since in the greater part of the world the number of esophageal adenocarcinomata is higher compared to squamocellular cancer, our study is of a special value. In our study only patients with locally advanced squamous cell oesophageal cancer were included which is a rarity in the literature. Our results are absolutely comparable to the results of similar studies in the literature. **(Table IV.)**

Table IV.: Comparison of our results with similar studies

Authors	Operated patients (number)	Resecta-bility (%)	R0 (%)	Operative mortality (%)	pCR (%)	2-year survival (%)	Median survival (months)
(1) Bidoli (n:34)	25	100	84	20	24	38	12
(2) Fink (n:55)	47	100	83	0	15	40	
(3) El Nakadi (n:61)	38	97	78	19	30	32	21
Present series (n:102)	82	86.5	83	16.9	24	32	12

III. SPECIALITIES IN THE TREATMENT OF CERVICAL OESOPHAGEAL CANCER

III.1 Introduction

The prognosis of upper oesophageal cancer is poor when compared to lower located tumors. These tumors often infiltrate neighbouring organs and surgical en-bloc resection is difficult, i.e. upper third cancers has the worst prognosis. It is especially true if the cancer is located around the pharyngo-oesophageal junction. This anatomical position of the tumour causes problems in the curative treatment. Namely, it is more difficult to perform a correct lymphadenectomy and the complications are also higher. The tumor can invade the neighbouring organs early (aorta, trachea), which especially in the cervical part results in irresectability, or in need for an extremely extended resection connected to high perioperative mortality rate. Besides the currently recommended resection margin for hypopharyngeal tumors and carcinomas of the cervical oesophagus is 2-3 cm, measured from the edge of the macroscopic tumor growth. It means that in cases of cervical oesophageal cancer the recommended resection is the pharyngo-laryngo-oesophagectomy which is accompanied by high morbidity and mortality (20-30%). The loss of the larynx causes a major reduction in the quality of life of these patients.

III.2 Patients and methods

Between Nov.1997 and Sept. 2005 102 patients were enrolled, which was reported above. Following the staging, patients received concomitant chemo-radiotherapy. After a four-week-long treatment free period restaging was carried out and patients considered resectable were submitted to surgery. Patients were divided into two groups. In Group 1 the tumor was located at the upper third of the oesophagus (above the aortic arch) in Group 2 the carcinoma was located in the mid third of the oesophagus (at or above the tracheal bifurcation) **(Table V.)**

Table V.: Clinical data

CLINICAL DATA	
Group I. n:40 (Upper third)	Group II. n:62 (Middle third)
Female/ male: 5/35	Female/male: 7/55
Mean age: 54 years (41-70)	Mean age: 57.11 years (41-73)
T3/T4: 21/19	T3/4: 24/38

III.3 Results:

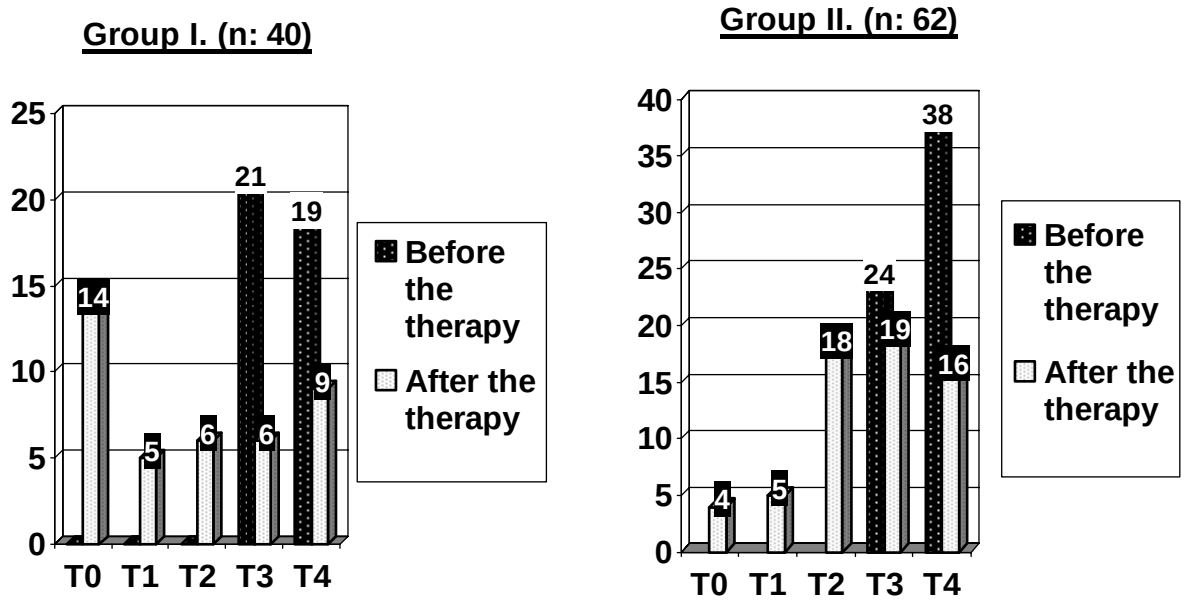


Figure 4: During the restaging a clear downsizing of the primary lesion was visible in both groups.

The resection rates were similar in the two groups (28/40; 70% and 43/62; 69%). The histopathological examination of the resected specimens confirmed pathological complete remission (pCR) in 14 patients in Group 1 (14/28, 50%) and in 3 patients in Group 2 (3/43, 7%), with a significant difference. ($p<0.001$).) The resectability rate was similar in the two groups (70% and 69%). In 70 % (28/40) of the cases with cervical oesophageal cancer, neoadjuvant chemo-radiotherapy induced partial or complete tumor regression that rendered pharyngo-laryngo-oesophagectomy unnecessary. During the surgical procedures in 18 cases the resection was performed with a transhiatal approach (Orringer procedure), in one case a transthoracic, McKeown operation was performed. In 15 cases larynx preserving oesophagectomy with partial pharyngectomy was performed. In 9 cases a pharyngo-laryngectomy was done combined with a segmental resection of the cervical oesophagus. Postoperative mortality was 14% (4/28), and postoperative morbidity was 43% (12/28) in Group 1. In Group 2 postoperative mortality was 18% (8/43) and postoperative morbidity was 62% (27/43). The differences were not significant.

Organ preserving procedures

1, Larynx preserving pharyngo-oesophagectomy

Those patients with a good response to treatment and tumour regression resulting in adequate safety margins to the larynx were submitted to total oesophagectomy and partial

pharyngectomy with preservation of the larynx, instead of a pharyngo-laryngo-oesophagectomy.

2,Laryngo-pharyngectomy with free jejunal transplantation

In cases when the cancer disappeared only from the cervical oesophagus, a pharyngo-laryngectomy was done. In these cases the pharyngo-laryngectomy was combined with a segmental resection of the cervical oesophagus and for reconstruction a free jejunal transfer was performed.

Statistical examintaions:

During the survival analysis the 2-years survival rate was 41%, the 4-years survival rate was 33%. A significantly improved survival was seen in cases with pCR, compared to the other cases. (p=0.024)

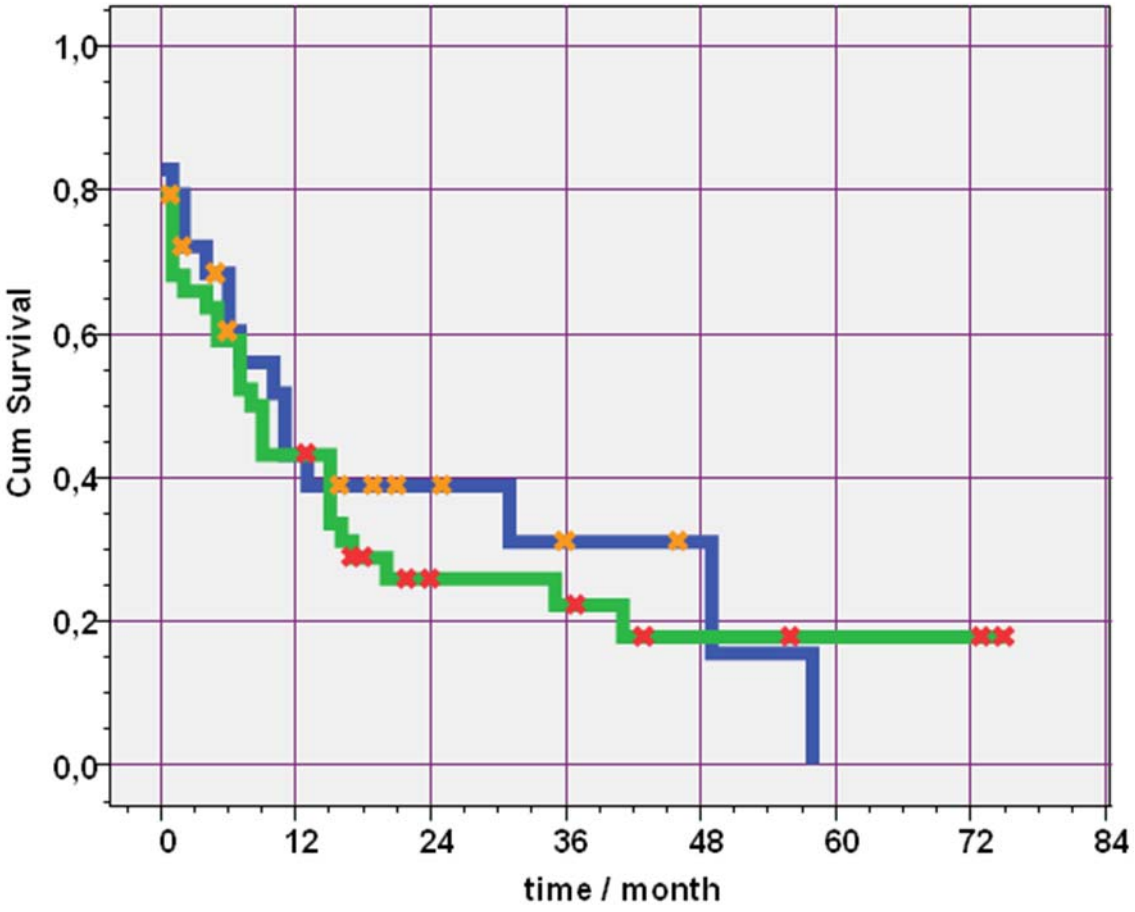


Figure 5.: The mean survival rate was not influenced by the location of the tumor as it was similar in Group 1 and Group 2. (p:0.67)

III.4 Discussion

In the treatment of oesophageal cancer the upper third tumors represent a critical localization, because a neoplasm in a less advanced stage usually requires more extensive surgery. This is one view why this group of oesophageal cancer patients can benefit the most from the multimodal treatment. During our investigation we proved, that upper third tumours are more responsive to neoadjuvant therapy, because significantly more pCRs were observed in patients with cancer located above the thoracic outlet (Group 1) compared to the mid third tumors (Group 2). Due to the major downsizing of the primary tumor, new organ preserving procedures could be performed. Since pCR results in statistically proven survival benefit, the higher location does not necessarily mean a disadvantage in the overall survival any more.

IV. Investigation of possible predictive markers

IV.1 Introduction

As we have seen, the preoperative chemo-radiotherapy combined with surgical resection improved the long term survival in locally advanced squamous cell oesophageal cancer. Nevertheless the neoadjuvant therapy raises further problems. One of the most important from these is to predict the response to the preoperative therapy. Unfortunately, not all of the patients respond to neoadjuvant therapy, and the survival of the nonresponders resected after neoadjuvant therapy is worse compared to those operated on without neoadjuvant therapy. This is why it would be important to identify those squamous-cell carcinoma cases that will benefit from neoadjuvant treatment, in order to avoid unnecessary toxicity, to lengthen survival and to ameliorate life quality. We can find many studies in the literature dealing with this topic, but at the moment we do not have a simple and practical predictor. The aim of our study was to investigate certain molecular-biologic markers as possible clinically useful predictors of response.

During oncological treatment the cytotoxic effect results in cell death through different pathways. We investigated different proteins which characterize the two major cell death pathways. The expression of anti-apoptotic proteins such as heat shock protein 90 (Hsp 90), small heat shock protein 16.2 (Hsp 16.2), Bcl-2 and proapoptotic protein Bax as well as the expression of necrosis-inducing SOUL protein were examined in esophageal tumor specimens prior to radiochemotherapy, to assess whether the expression of these proteins can be used to divide patients into groups with favorable or unfavorable response to treatment. The other aim of our work was to explain the different response to the neoadjuvant therapy of oesophageal tumors on different locations

IV.2. Patients and methods

Twenty patients with esophageal cancer, candidates for neoadjuvant radiochemotherapy, were enrolled in the study between 2005 and 2006. All patients had squamous-cell cancer, with stages cT3-4, cN0-1, cM0, located in the upper two-thirds of the esophagus. (Table 1) All signed the informed consent, which was approved by our Local Ethics Committee.

Staging procedures included endoscopy with biopsy, endoscopic ultrasound, computed tomography (CT) scan of chest and abdomen and bronchoscopy. From each patient biopsy was taken from the tumor as well as from the intact part of the esophagus. Twenty samples of squamous-cell esophageal cancer and twenty samples of normal esophageal tissue were examined by Western-blot method. The expression of Hsp90, Hsp 16.2, SOUL protein, Bax and Bcl-2 proteins and the Bax/Bcl-2 ratio were examined in relation to the clinical response. The tumor-free specimens served as controls. Patients then received external-beam therapy (total of 36 to 40 Gy, fraction dose:1.8 Gy) and concomitant chemotherapy during the first week of irradiation: cisplatin (100 mg/m2 intravenously on day 1) and 5-fluorouracil (1000 mg/m2/day, continuous intravenous infusion through days 1.-5.) Four weeks after the completion of radiochemotherapy, clinical response to treatment was assessed according to the RECIST criteria.(control CT scan and endoscopy with biopsy). (9) Six to nine weeks after neoadjuvant therapy if there was no evidence of disease progression, patients underwent definitive surgical resection. Pathological response to treatment was determined by the histologic evaluation of the resected specimen. Side-effects were documented in conformity with the Common Terminology Criteria for Adverse Events, Version 3.0.

IV.3 Results

Clinical results

In this study a total of 20 patients with locally advanced squamocellular cancer recieved neoadjuvant chemo-radiotherapy. **(Table VI.)**

Table VI: Clinical data

	Median
Age (years)	60 (41-69)
Distance from teeth (cm)	25 (17-31)
Male/Female	16/4
T3/T4	11/9
N0/N1	6/14
Resection	13/20
R0 resection	9

A 65% clinical response rate was found. One patient had complete remission (5%), 12 patients had partial remission (60%), 5 patients had stable disease (25%), 1 patient had progressive disease (5%) and 1 patient died during the treatment (5%). During the oncological treatment grade 3 or 4 gastrointestinal, hematologic and pulmonary side-effects occurred, one patient died due to severe sepsis. Patients with complete or partial remission underwent definitive surgery. The following histological response was observed: no residual tumor tissue in 2 patients (10%), partial remission in 11 cases (55%), respectively. Altogether 13 surgical resection were performed and R0 resection was possible in 9 cases (70%). There was no perioperative mortality.

Detection of possible new markers by Western-blot

The tumor samples from patients with no clinical response contained approximately double the amount of Hsp 90 and Hsp 16.2, which is statistically significant (p=0.049 and p=0.019). They also expressed SOUL at a higher level and had a lower Bax/Bcl-2 ratio than those with good clinical response, but these results were not significant (p=0.247 and p=0.883). **(Figure 6.)**

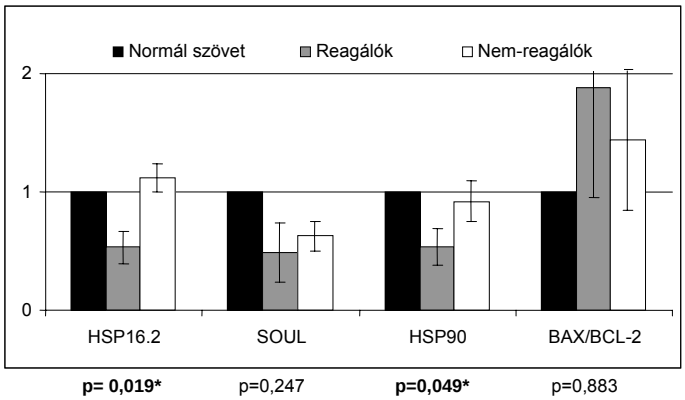
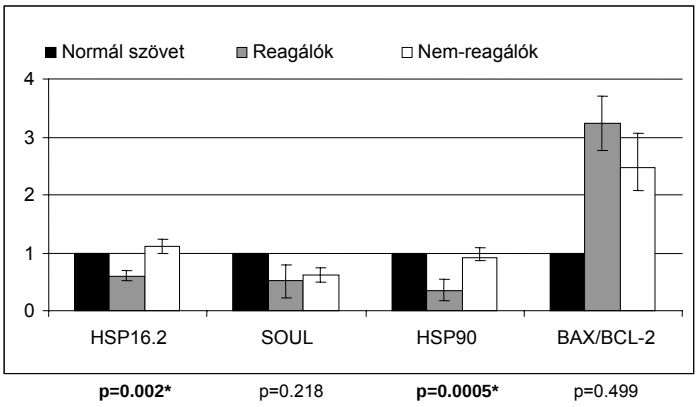


Figure 6.: Levels of tumor-associated proteins and clinical response (* means p<0.05, which is statistical significance)

Results of the pathologic examination correlated with the clinical results. **(Figure 7.)**

Figure 7: Levels of tumor-associated proteins and pathological response (* means p<0.05, which is statistical significance)



Particularly interesting results were observed when samples were divided according to the tumor locations. Upper part tumors expressed chaperone proteins in significantly lower amounts than tumors located in the lower part of the esophagus (Hsp90 upper vs. middle p=0.006 and Hsp16.2 upper vs. middle p=0.012). The SOUL protein was also expressed in significantly smaller amounts in the upper half of the esophagus (p=0.047). Although the Bax/Bcl-2 ratio seemed to be lower in the middle-third tumors, the difference was not significant (p>0.05). **(Figure 8.)**

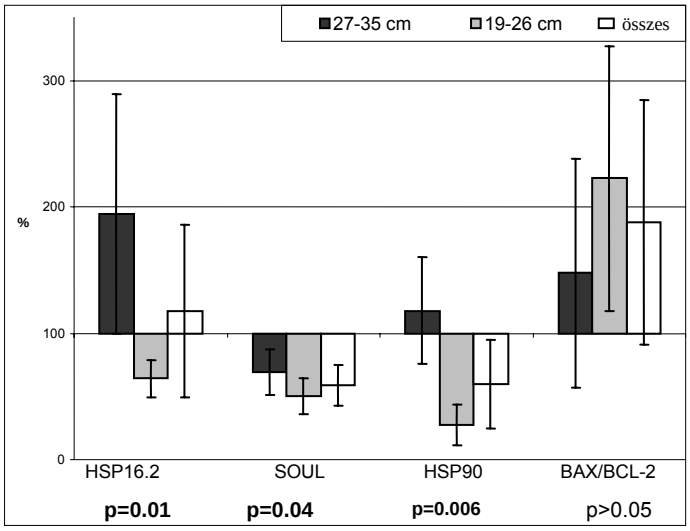


Figure 8.: An apparent difference was observed according to the various tumor locations

IV. 4 Discussion

A number of recent studies have attempted to identify markers that could be used to predict clinical response to neoadjuvant therapy. (metabolic response evaluation with PET, gene expression arrays etc.) Our results also suggest that response to preoperative RCT may be related to a different activation of stress mechanisms which act through different signal transduction pathways. Our encouraging data imply that protein expression profiling may distinguish patients with a different response to radiochemotherapy. Evaluation of the expression of tumor associated proteins from endoscopic biopsy specimens could serve as a good predictor of response to RCT and it could contribute to better patient selection. (at higher Hsp level the neoadjuvant treatment is inefficient) This is an important finding, because with the help of a proper predictive marker an individualised therapy could be administered and in non-responsive cases the surgical therapy could be performed without any delay.

Besides, our observation, that upper-part esophageal tumors express Hsp-s at significantly lower levels than middle-third tumors, is of particular importance, since it may be the possible explanation to the widely known fact, that cervical esophageal cancer has a superior sensitivity to multimodal therapy. It may suggest that upper third tumors should be treated differently compared to lower localized cancer. However, verification of this thesis and the potential of these proteins as biomarkers of response warrants further validation.

V. Summary of new findings

1. Preoperative chemo-radiotherapy in Hungary was firstly introduced by us in the treatment of locally advanced oesophageal cancer.
2. In a retrolective study we proved, that neoadjuvant chemo-radiotherapy improved the long term survival of these patients, and that patients with pathological complete response (pCR) had significantly better survival compared to all the others.
3. We also confirmed, that upper third tumours are more responsive to neoadjuvant therapy, because significantly more pCRs were observed. Since pCR results in statistically proven survival benefit, a former conception could be modified, thus the higher location of the tumor does not necessarily mean a disadvantage in the overall survival any more.
4. In cases of a cervical oesophageal cancer due to a major downsizing of the primary tumor, new organ preserving resections could be performed. These procedures improved the quality of life and did not decrease the long time survival.
5. In a prospective study we investigated different proteins which characterize the two major cell death pathways. Our observations suggest, that these proteins could serve as good predictors of response.
6. This observation may be a possible explanation for the detected and significantly higher pCR rate in cervical esophageal cancer. It may suggest, that on the basis of a different tumour biology, cervical oesophageal cancer has a distinct behaviour compared to lower oesophageal cancer.

VII. ACKNOWLEDGEMENTS

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VIII. Publications and presentations

Presentations in connection with Thesis

Hungarian

1. **A. Papp**, L. Cseke, G. Horváth: Complete pathological remission after neoadjuvant therapy in T4N1 squamous cell oesophageal cancer, Fiatal Sebészek Angol Nyelvű Fóruma, Szeged, 1998

2. **Papp A**, Cseke L, Varga G, Kalmár K, Horváth G, Horváth ÖP: Az előrehaladott nyelőcsőrák neoadjuváns kezelése A Magyar Kemoterápiai Társaság XIV. Konferenciája, Hajduszoboszló, 1999

3. **Papp A**.,Cseke L,Varga G,Kalmár K,*Horváth G, Horváth ÖP Az előrehaladott nyelőcsőrák neoadjuvans kezelése Fiatal Onkológusok Fóruma, Pécs,2001

4. **Papp A**, Cseke L, Varga G, Horváth G, Horváth ÖP Felső és középső harmadi nyelőcsőrákok neoadjuváns kezelési eredményeinek összehasonlító vizsgálata MST Kongresszus, Budapest, 2002

5. **Papp A**., Cseke L., Horváth G., Horváth Ö.P. Felső és középső harmadi nyelőcsőrákok neoadjuváns kezelési eredményeinek összehasonlító vizsgálata MGT 45. Nagygyűlése, Balatonaliga, 2003

6. **Papp A**, Cseke L, Varga G, Kalmár K, Horváth G, Márton S, Horváth ÖP Előrehaladott nyelőcsőrákok neoadjuváns kezelésével szerzett tapasztalataink – a felső harmadi daganatok jobban reagálnak? MGT 46. Nagygyűlése, Balatonaliga, 2004

7. **Papp A**., Cseke L., Varga G., Kalmár K., Márton S., Horváth G., Pótó L. , Horváth Ö.P. Rosszindulatú nyelőcsődaganatok miatt végzett reszekciók klinikánk anyagában MST Kongresszus, Pécs, 2004

8. **Papp A**, Cseke L, Ésik O, Horváth ÖP A neoadjuváns chemo-radiotherapia javítja a túlélést előrehaladott nyelőcső laphámrákok esetén MST Kísérletes Sebészeti Szekció XX. Jubileumi Kongresszusa, Hajduszoboszló, 2005

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