Original Article

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Benefits and Disadvantages of Neoadjuvant Radiochemotherapy (RCT) in the Multimodal Therapy of Squamous Esophageal Cancer (ESC)

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Rezumat

Beneficii și dezavantaje ale radiochimioterapiei (RCT) neoadjuvante în terapeutica multimodală a cancerului scuamos esofagian (ESC)

Introducere: Scopul lucrării este de a prezenta avantajele și dezavantajele RCT cu caracter neoadjuvant în terapia multimodală a ESC.
Material și metodă: Între anii 1998-2014 au fost tratați 221 de pacienți cu ESC dintre care 85 au beneficiat de RCT neoadjuvantă. Acestora li s-a făcut evaluarea imagistică și patologică a răspunsului pe baza criteriilor RECIST și MANDARD iar datele s-au interpretat statistic din punct de vedere al factorilor care au influențat răspunsul. De asemenea, s-au evaluat corelațiile statistice intre RCT și rezecabilitate, morbiditate postoperatorie, mortalitate și supraviețuirea la distanță.
Rezultate: 45 pacienți au fost responderi imagistici și s-au operat 34, 40 non-responderi din care s-au operat 14. Din cei 48 de pacienți operați cu RCT preoperator evaluarea histopatologică a arătat că responderi patologici au fost 32 și non – responderi, 16. Au fost analizate statistic corelațiile dintre RCT și rezecabilitatea, stadiul, localizarea ESC, morbiditatea, mortalitatea și supraviețuirea.
Concluzii: RCT creşte rezecabilitatea, îmbunătăţeşte supraviețuirea şi durata maximă de supraviețuire mai mult în cazul responderilor decât al non-responderilor şi nu influențează complicațiile postoperatorii şi mortalitatea postoperatorie, nici în rândul responderilor şi nici al non-responderilor. Rezultatul evaluării imagistice a răspunsului la RCT supraevaluează responderii.

Cuvinte cheie: radiochimioterapie neoadjuvanta, beneficii și dezavantaje, tratament cancer esofagian scuamos

Abstract
Introduction: The purpose of this paper is to present the advantages and disadvantages of neoadjuvant RCT in multimodal therapyof ESC.
Material and method: Between 1998-2014 221 patients were treated with ESC, 85 of whom received neoadjuvant RCT. For these we have made imaging and pathologic assessment of response using RECIST and MANDARD criteria and statistical data were interpreted in terms of the factors that influence the response. Also, they were evaluated statistical correlations between RCT and resectability, postoperative morbidity, mortality and long-term survival.
Results: 45 patients were imagistic responders and 34 underwent surgery, 40 non-responders of which 14 underwent surgery. Of the 48 surgical patients with preoperative RCT, histopathological evaluation showed that 32 were pathological responders and 16 non – responders. There were performed statistical

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analyzes of correlations between RCT and resectability, stage, location of ESC, morbidity, mortality and survival.
Conclusion: RCT increase resectability, improves survival and maximum duration of survival, more in responders than in non-responders and does not affect postoperative complications and postoperative mortality, nor among the responders or non-responders. Imaging evaluation result of the response to RCT overestimate responders.

Key words: neoadjuvant radiochemotherapy, benefits and disadvantages, treatment esophageal squamous cancer

Introduction

Esophageal squamous cell carcinoma (ESC) is a disease with increasing incidence and, despite progress in the diagnosis and treatment of this disease, prognosis remains unfortunately very poor. It is one of the most aggressive solid tumors with a mean survival not exceeding 5% in 10 years.

If the disease is strictly localized, the best local disease control is realised by R0 tumor resection with abdominal and mediastinal lymphatic dissection. In cases with locally advanced squamous cell carcinoma that receive only surgical treatment, the longterm results are modest, imposing on multimodal therapeutic approach. Multimodal treatment of this disease is part of overall efforts to optimize results and increase survival and quality of life of these patients because currently there isn't an opinion unanimously accepted regarding the indications of this therapy, nor a standard in management of the disease that assumes a good response of ESC to radiochemotherapy.

The purpose of this paper is to determine the advantages and disadvantages of neoadjuvant radiochemotherapy in the management of patients with esophageal squamous cell carcinoma, knowing that not all patients respond favorably to this therapy, and of those who respond not all recorded the same type of response (complete or incomplete).

Material and Method

In St. Mary Hospital in General and Esophageal Surgery Clinic, between 1998 and 2014 were hospitalized and treated 221 patients with ESC in different developmental stages. Cases were selected on the grounds of histopathology after endoscopic biopsy - squamous cell carcinoma; the exclusion criterion was adenocarcinoma. Of the 221 patients with ESCC we excluded patients with stage IV (72 patients) and 149 patients remained in stages 1, 2, 3; among these, 85 performed preoperative RCT (57%) and 64 have not.

The 85 patients with neoadjuvant RCT were evaluated imagistic and divided in responders and non-responders (RECIST assessment in accordance with the Guidelines for Clinical and pathologic Studies on Carcinoma of the esophagus 9 th. Ed. 24) at 30 days pre and post-therapy:

Complete Responders (CR)

Complete macroscopic disappearance of primary tumor and secondary lesions and non-appearance of new lesions;

Partial Responders (PR)

Decrease by 30% of maximum size of the tumor; Lack of progression in primary or secondary lesion size; Non-occurrence of new lesions;

No Change (NC)

Unsignificant dimensional variations - minimal changes; The lack of tumor progression and the appearance of no new lesions;

Progressive Disease (PD)

Increase of at least 20% of the maximum tumor size, number of lesion progression of secondary lesions, appearance of new lesions;

Of those 85, 48 were operated about after a month from completion of the RCT (34 responders and 14 non-responders); these were also evaluated regarding the pathological response by histopathological study of specimens after resection [Mandard Classification and Mandard modified Classification (1)]: Complete response: no tumor cells found on specimens of resection and no lymphatic metastases; Partial answer: less than 10% viable tumor cells per examination field; No answer: more than 10% viable tumor cells per examination field.

The other 37 patients with neoadjuvant RCT (11 considered responders after imagistic evaluation and 26 non-responders) could not benefit from surgery either due to disease progression, or because of impaired general condition or longer wanted the intervention.

Initial therapeutic protocol included induction chemotherapy with 5-FU and cisplatin along with radiotherapy 40 Gy in 20 fractions (2,3). Patients were evaluated imagistic 30 days before the RCT and 30 days post-RCT as following: Endoscopy (video) with biopsy (EDS), echoendoscopy (EUS), barium meal, computed tomography (CT), explorations on which we have performed assessments related to the imagistic response, patients were divided into responders (complete responders - CR, partial responders - PR) and non-responders (progressive disease - PD, stationary disease - NC).

This assessment of response was followed by statistical interpretation of the data obtained and looked for statistically significant associations between different types of response and location, ESC staging. Along with the 48 patients operated in the group of 85 with initial RCT, underwent resectional surgery another 11 patients in the group of 64 without preoperative RCT, so from the 149 patients std.1, 2, 3 were operated in total 59 (48 with and 11 without RCT). Regarding the gender distribution of the 221 patients with ESCC, we found a predominance of men with a ratio of 5.5 / 1, the mean age was 59.09 years with extreme values of 41 and 82 years and the most frequent location was medio-thoracic. Clasification on stages showed that most commonly encountered has been the stage 3 (117 cases), followed by stage 4 (72 cases), stage 2

(28 cases) and stage 1 in 4 cases. The types of surgical interventions: subtotal (EST) and total (ET) esophagectomy (59 cases), gastrostomy, jejunostomy or bypass with colon passed retrosternal or presternal for palliation of dysphagia (in the 162 cases: 37 of the 85 with neoadjuvant RCT without surgery + 53 of the patients without neoadjuvant RCT + 72 patients with metastatic disease), and lately for treatment of dysphagia were installed endoscopic stents. Approach paths used for esophageal resections were cervico-abdominal (AC) and toracofrenolaparatomy (TFL) in the lower thoracic locations (TFL just at the beginning), cervico-thoracic (TC) - in the initial period, cervico-thoraco-abdominal (TAC) in medio-thoracic and cervical locations.

We have followed than how neoadjuvant RCT influenced resectability, postoperative complications (anastomotic fistula, pulmonary complications and stenosis), postoperative death and survival in the distance, to landmark date 1 January 2015. To achieve this we used methods of statistical interpretation of data searching to find the existence of statistically significant correlations.

Imagistic evaluation of the effectiveness of neoadjuvant RCT therapy in ESC

We have used videoendoscopic evaluation for diagnosis (together with biopsy) (4), and also for assessing the presence or absence of response (5) but necrosis post-radiotherapy and the fibrotic modifications sometimes prevented a proper biopsy (6). We determined tumor size and extend its before and after RCT, on the same patient (*Fig. 1*).

Barium meal was used in assessing the response, comparing the length of malignant esophageal stenosis pre and post therapy in the same patient (*Fig. 2*).

We used tomographic evaluation, the standard method for assessing response to RCT (7) but with a lower value in determining pathologic response (8), to compare the maximum tumor diameter before and after RCT (*Fig. 3*).

EUS evaluation we used in assessing the response by measuring tumor size, degree of parietal infiltration and lymph condition (9,10) (*Fig. 4*). The limitation of the method are tumors that cannot be passed with the endoscope; sometimes were required esophageal dilatation sessions before performing EUS.

Results

Imagistic evaluation of the response to neoadjuvant RCT

Of the 85 with neoadjuvant RCT, 45 patients (53%) met the imaging criteria of response (CR + PR), of which CR 7 patients (8.3%) and 38 PR (44.7%). Non responders on imagistic criteria (NC + PD) were 40 (47%), 23 patients NC (27%) and 17 patients PD (20%) (*Fig. 5, Fig. 6*).

Evaluation of the type of response to RCT depending on the location of ESC. Regarding the location of the ESC in the 85 patients who did neoadjuvant RCT, 17 patients had cervical location (C), 46 medio-thoracic location (M) and 22

Figure 1. *Videoendoscopy image post neoadjuvant RCT in responder group in the same patient: reduction in tumor volume and of the extent of the tumor – collection of images of our clinic*

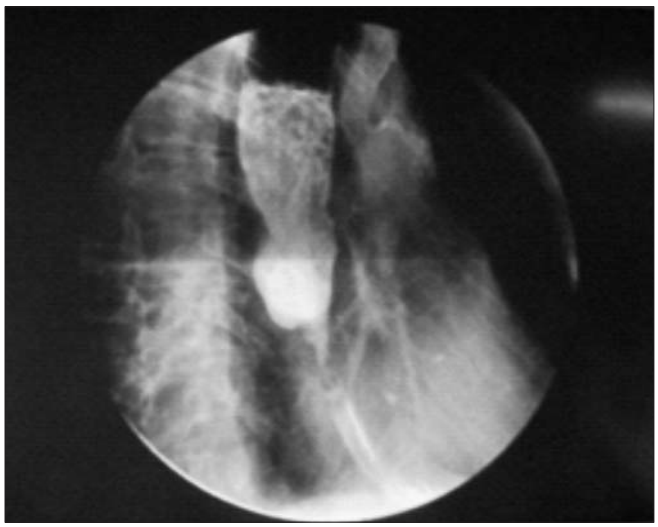

Figure 2. *Esogastroduodenal barium meal post neoadjuvant RCTthe non-responder group: determine the length of tumor stenosis - collection of images of our clinic*

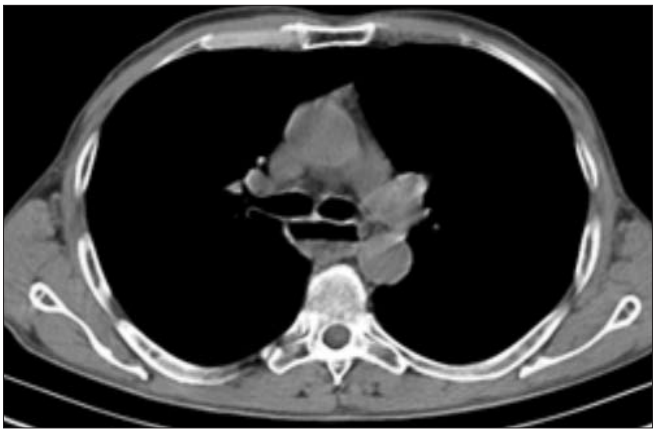

Figure 3. *CT image after neoadjuvant RCT in responders group - collection of images of our clinic*

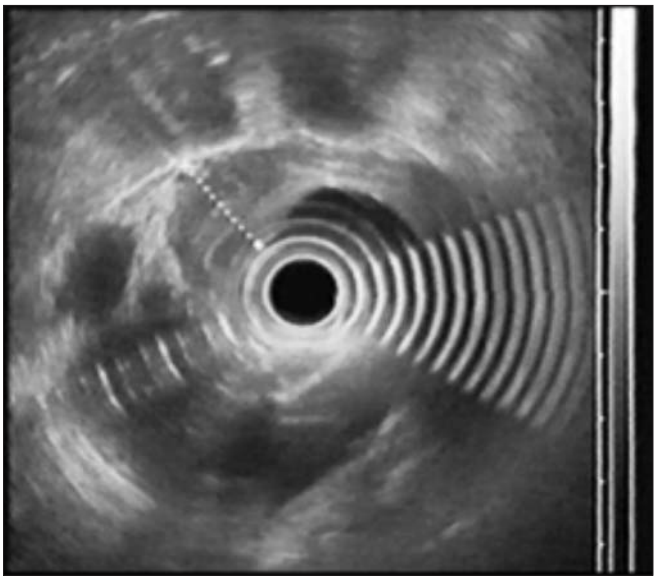

Figure 4. *EUS determination of tumor size after RCT in group of non responders - collection of images of our clinic*

Figure 7. *The types of response to RCT for the C, M, T location of the ESCC – the most responsive tumors are localized medio-thoracic, the less responsive are those with cervical location*

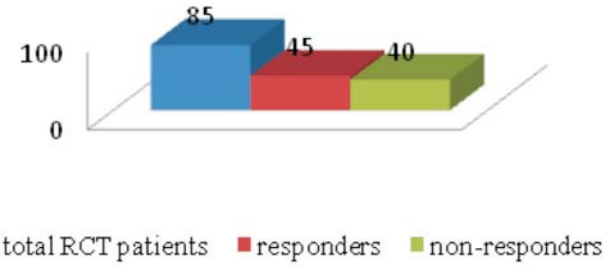

Figure 5. *Number of imagistic responders to neoadjuvant RCT*

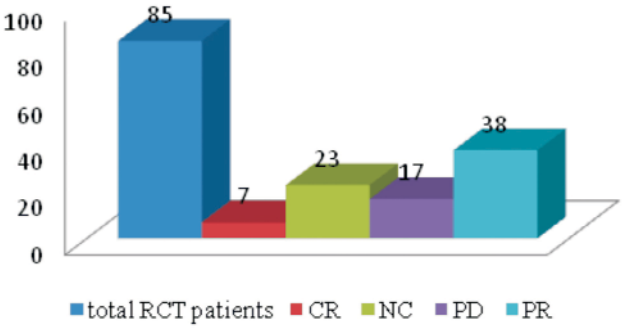

Figure 6. *The types of imaging response in patients with neoadjuvant RCT*

lower thoracic location (T). The types of response depending on location are shown in *Fig. 7* and we found a association between response type and location (p value = 0.032782), *Table 1*.

Assessment of the response type to RCT depending of the stage of ESC

Stage of tumors of 85 patients with neoadjuvant RCT is as

Table 1. *Significant correlation between types of response (CR and PR) and location M of ESCC- p value = 0.032782 differences in percent of responders for medio-thoracic localization are significant compared to the cervical and lower thoracic of ESCC:*

Crosstab

Location of ESCC		TYPE_RESP				Total
		CR	NC	PD	PR	
C	Count	1a	7a	5a	4a	17
	% within TYPE_RESP	14.3%	30.4%	29.4%	10.5%	20.0%
M	Count	6a	10a	5a	25a	46
	% within TYPE_RESP	85.7%	43.5%	29.4%	65.8%	54.1%
T	Count	0a	6a	7a	9a	22
	% within TYPE_RESP	0.0%	26.1%	41.2%	23.7%	25.9%
Total	Count	7	23	17	38	85
	% within TYPE_RESP	100.0%	100.0%	100.0%	100.0%	100.0%

Each subscript letter denotes a subset of TIP_RASP categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Likelihood Ratio, p value= 0.032782

Table 2. *Statistically significant association between the type of response and tumor stage (p value = 0.000009)*

Crosstab						
Tumor stage		**TYPE_RESP**				**Total**
		CR	**NC**	**PD**	**PR**	
1	Count	0a	1a	0a	1a	2
	% within TYPE_RESP	0.0%	4.3%	0.0%	2.6%	2.4%
2	Count	7a	3b	0b	12b	22
	% within TYPE_RESP	100.0%	13.0%	0.0%	31.6%	25.9%
3	Count	0a	19b, c	17c	25b	61
	% within TYPE_RESP	0.0%	82.6%	100.0%	65.8%	71.8%
Total	Count	7	23	17	38	85
	% within TYPE_RESP	100.0%	100.0%	100.0%	100.0%	100.0%

Each subscript letter denotes a subset of TYPE_RESP categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Likelihood Ratio, p value=0.000009

Table 3a. *Evaluation of imagistic response (preoperative) for the 48 patients with ESCC with surgery*

IMAG RESP TO RCT (RECIST)	Total N
YES	34
NO	14
Overall	48

Table 3b. *Pathological evaluation of response (postoperative) for the 48 patients with ESCC with surgery*

IMAG RESP TO RCT (RECIST)	Total N
PATH RESP to RCT (MANDARD)	Total N
YES	32
NO	16
Overall	48

follows: 2 cases of stage 1, 22 cases stage 2, 61 cases stage 3. We found an association between the type of response and stage, p value = 0.000009, Likelihood Ratio Test - Table 2: Differences of percentages significant for stage 2: CR (100%) and NC (13.0%), CR (100%) and PD (0.0%), Differences of percentages for stage 3: CR (0%) and NC (82.6%), CR (0%) and PD (100%), PD (100%) and PR (65.8%).

Of the 85 patients with neoadjuvant RCT, 45 have met the criteria of imaging response and 40 have not; 48 patients underwent surgery (34 of those who had imagistic response and 14 of those who have not responded) - *Table 3A*. The 48 patients that received surgery in addition to clinical and imaging post-RCT also received a postoperative pathologic evaluation (modified MANDARD classification). The number and types of pathological response were: 4 patients with complete pathological response (4.7%), 28 patients partial response (ie a total of 32 responders), 16 patients without response (*Table 3B*), response that is different from the result by imagistic evaluation: 34 responders (CR + PR) and 14 non-responders (NC + PD).

Immunohistochemical issues detected in patients with ESC treated with neoadjuvant RCT. In the group of non-responders we found overexpression of p53, c-erbB-2 presence

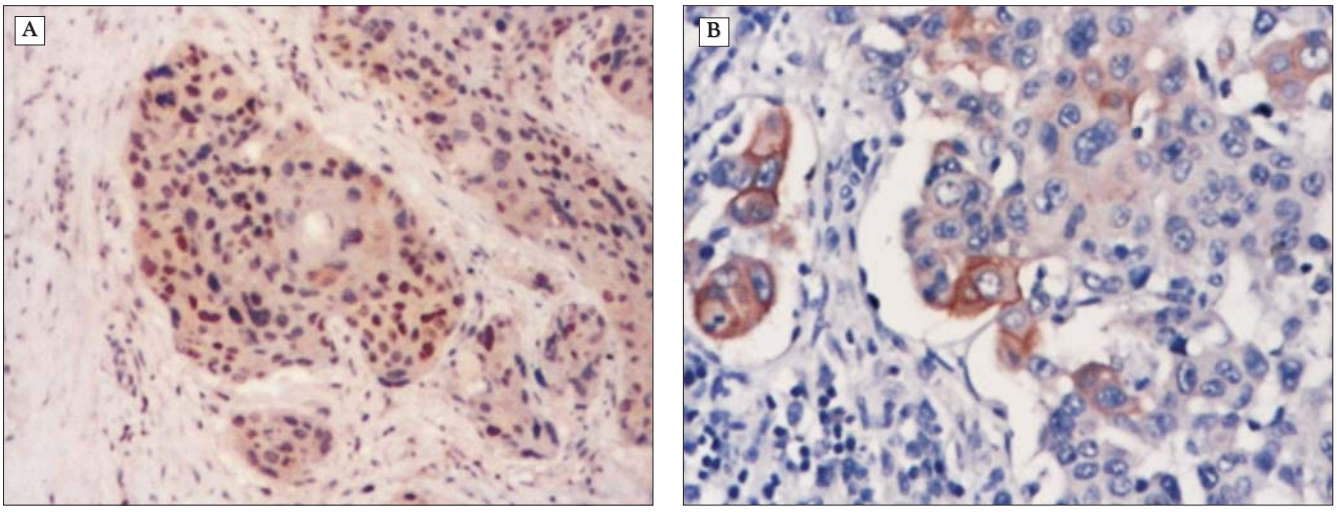

Figure 8. ***(A)*** *Overexpression p53 (+) 30%, 10x (group of non-responders - gallery of clinic);* ***(B)*** *c-erB-2 presence (+), 20x, (group of non-responders - gallery of clinic)*

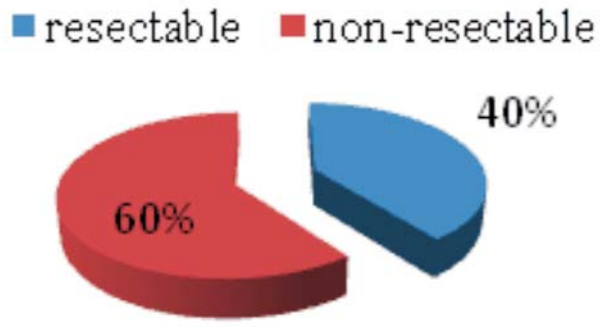

Figure 9. *Global rate of resectability for the 149 patients*

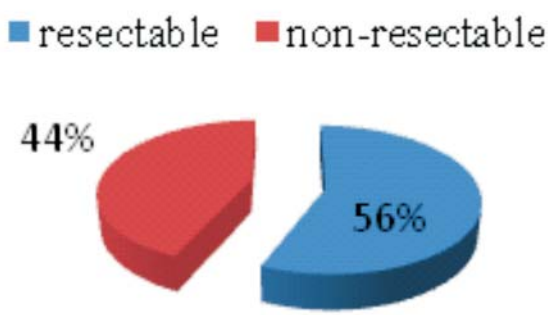

Figure 10. *Rate of resectability in the group of patients with neoadjuvant RCT*

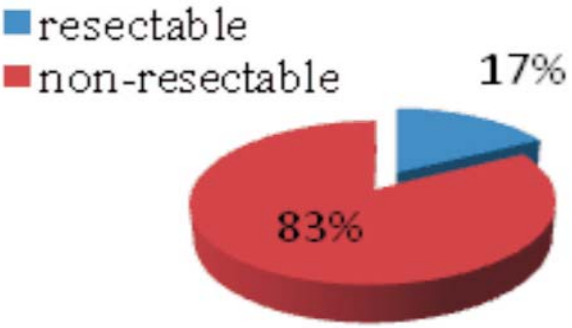

Figure 11.

and expression of tumor proliferation marker Ki-67 (*Fig. 8a, Fig. 8b* - the group of non-responders).

Influence of neoadjuvant RCT on resectability

Of the 149 patients in stage 1, 2, 3, 59 have been operated, the rate of resectability was 40% (*Fig. 9*).

Not all patients who benefited from RCT were operated, but only 48 of the 85 with neoadjuvant RCT (*Fig. 10*).

Of the 64 patients without RCT 11 were operated at a rate of resectability of 17% (*Fig. 11*)

Of the 85 patients with neoadjuvant RCT were 45 responders and 40 non-responders. Of the 45 responders patients 34 were operated (76%), and from 40 non-responders 14 were operated (35%) (*Fig. 12A, Fig. 12B*)

The association between imagistic response to RCT and resectability. Within the 48 patients operated, the percentages of those who answered imaging operations differ significantly from the percentage among those who did not respond, p value = 0.000167, *Table 4*.

Global resecability in group of 149 patients in stages 1, 2, 3 was 40% , among those with RCT was 56% and for those who have responded to treatment was 76% (non -responders had a rate of 35%), while resectability among those without neoadjuvant RCT was 17%, so neoadjuvant RCT improves resectability, and in responder group significantly increases resectability (p value <0.05).

The association between resectabilityand location of ESC showed an association between them (value = 0.024770), significant differences between the percentages of operations for C location (35.3%) and M location (69.6%) *Fig. 13, Table 5*.

The association between ESC stage and surgery (resectability) for 48 patients with ESC who received RCT showed that there was statistical significance (p value = 0.047882). Resecability correlate with tumor stage, so the two patients in stage 1 were both operated (100%), of the 22 patients in stage 2 - 16 were operated (72.7%) and of the 61 patients in

Table 4

Crosstab

			SURGERY_YES/NO		Total
			YES	NO	
RASP	YES	Count	34a	11b	45
		% within OPERATIE_DANU	70.8%	29.7%	52.9%
	NO	Count	14a	26b	40
		% within OPERATIE_DANU	29.2%	70.3%	47.1%
Total		Count	48	37	85
		% within OPERATIE_DANU	100.0%	100.0%	100.0%

Each subscript letter denotes a subset of OPERATIE_DANU categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Pearson Chi-Square, p value=0.000167

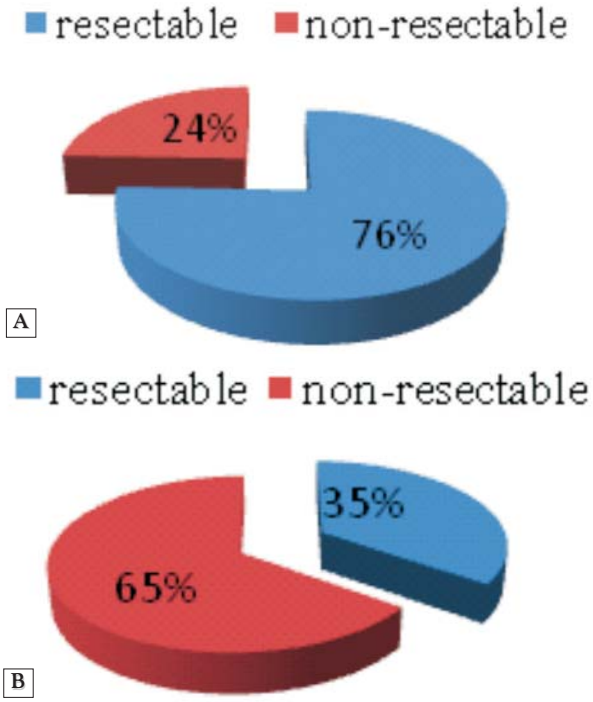

Figure 12. *(A) - Rate of resectability for reponders;* ***(B)*** *- Rate of resectability for non-reponders*

stage 3 - 30 patients were operated (49.2%) - *Table 6*.

Resecability according to the degree of invasion parietal (T). Regarding the degree of parietal invasion (T), there is an association between T and surgical intervention in the group with neoadjuvant RCT, significant differences between stage T2, T3 (66.7%) and T4 (26.1%), p value = 0.003465 - *Fig. 14 Table 7*.

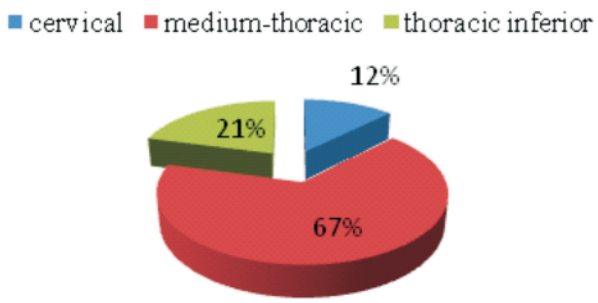

Figure 13. *Resecability depending on the location of ESC in patients who have received neoadjuvant RCT significantly better for medio-thoracic location*

Results of surgical treatment

Analysis of postoperative complications in patients with ESC with and without neoadjuvant RCT. Postoperative complications most important that we encountered were pulmonary, fistular and stenotic and from the 59 patients with surgery (48 with and 11 without RCT) there were complication in 31 patients (52.5%).

Table 5

Crosstab

			LOC			Total
			C	M	T	
SURGERY_YES/NO	DA	Count	6a	32b	10a, b	48
		% within LOC	35.3%	69.6%	45.5%	56.5%
	NU	Count	11a	14b	12a, b	37
		% within LOC	64.7%	30.4%	54.5%	43.5%
Total	Count		17	46	22	85
	% within LOC		100.0%	100.0%	100.0%	

Each subscript letter denotes a subset of LOC categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Pearson Chi-Square, p value=0.024770

Table 6

Crosstab

			STADIU			Total
			1	2	3	
SURGERY_YES/NO	YES	Count	2a	16a	30a	48
		% within STADIU	100.0%	72.7%	49.2%	56.5%
	NO	Count	0a	6a	31a	37
		% within STADIU	0.0%	27.3%	50.8%	43.5%
Total	Count	2	22	61	85	

Each subscript letter denotes a subset of STADIU categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Likelihood Ratio, p value=0.047882

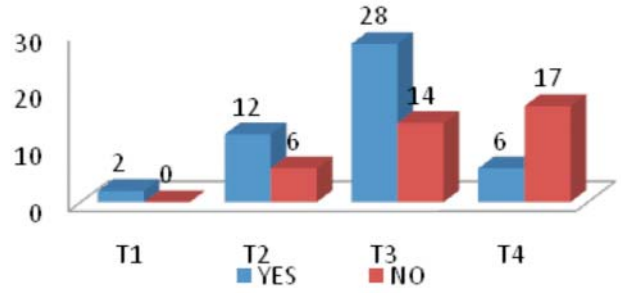

Figure 14. *Resecability depending on the stage T of patients with neoadjuvant RCT, significantly better for T2 and T3 versus T4*

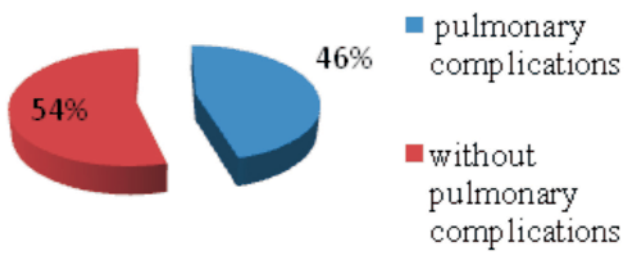

Figure 15.

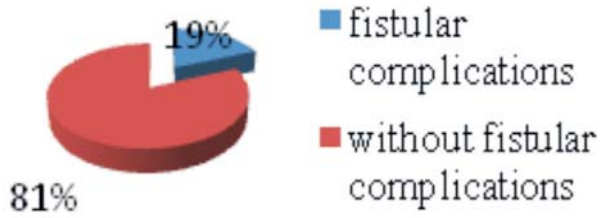

Figure 16.

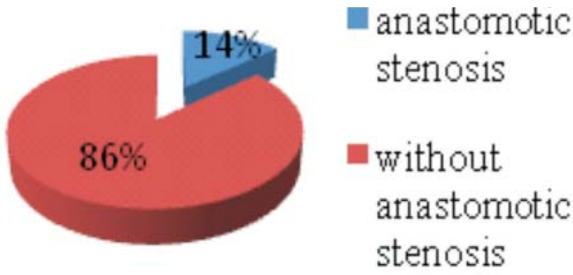

Figure 17.

Pulmonary complications were encountered in 27 of the 59 operated patients (46%) - *Fig. 15*.

Fistular complications were encountered in 11 of the 59 operated patients (19% - mainly cervical fistula) - *Fig. 16*.

Anastomotic stenosis was the third major complication we met in 8 of the 59 patients operated with ESC (14%) - *Fig. 17*.

Pulmonary complications and type of pathologic response to neoadjuvant RCT. Of the 32 patients with pathologic response (RASP Yes) 13 developed pulmonary complications (41%) (*Fig. 18A*) and in 16 patients without pathologic response (RASP No) 8 developed complications (50%) (*Fig. 18B*), the difference was not significant (p value = 0.555283).

Pulmonary complications were met in 46% of all 59 patients with surgery. The rate of this complication in 48 patients with neoadjuvant RCT was 44%, in responders 41%, and in non-responders 50%, which is lower in patients with RCT and especially in the responder, compared to general rate, without being statistically significant.

Anastomotic fistula was met in 11 patients in the study group of 59 patients (19% mainly cervical fistula).

Fistular complications and type of pathologic response to neoadjuvant RCT. Of the 48 patients who met the criteria of imagisti response (RESP Yes) 9 patients had fistulas (28%) and in the group of those who have not responded (RCT No) only one patient had fistula (6%) (*Fig. 19A*, *Fig. 19B*), the difference was not significant (p value = 0.132212).

Fistular complications were met in 19% of surgical patients (mainly cervical), and the rate of this complication in patients with neoadjuvant RCT was 21%, 28% in pathological responders and 6% in non-responders, so the rate was higher than the global for those with RCT and responders without detecting statistically significant differences.

Regarding stenosis, this occurred in 8 patients of the 59 with surgery for ESC (14%).

Table 7

Crosstab

			T				Total
			1	2	3	4	
SURGERY_YES/NO	YES	Count	2a, b	12a, b	28b	6a	48
		% within T	100.0%	66.7%	66.7%	26.1%	56.5%
	NO	Count	0a, b	6a, b	14b	17a	37
		% within T	0.0%	33.3%	33.3%	73.9%	43.5%
Total	Count	2	18	42	23	85	
	% within T	100.0%	100.0%	100.0%	100.0%	100.0%	

Each subscript letter denotes a subset of T categories whose column proportions do not differ significantly from each other at the .05 level.
Test: Likelihood Ratio, p value=0.003465

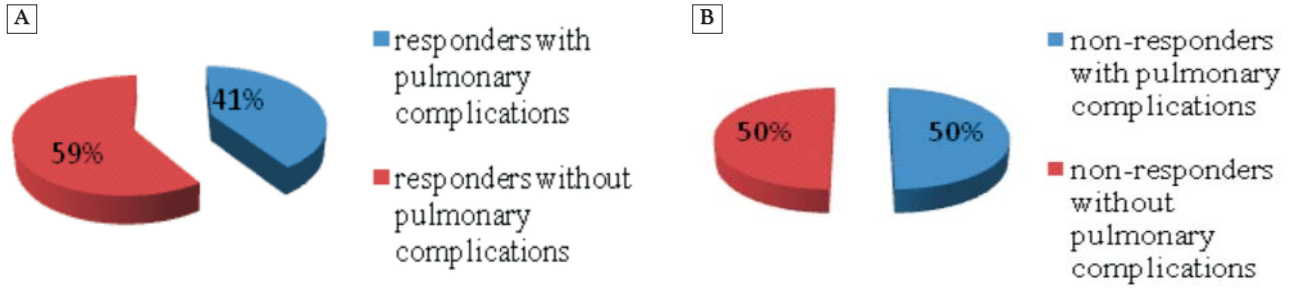

Figure 18. ***(A)*** *- Pulmonary complications in responders;* ***(B)*** *- Pulmonary complications in non-responders*

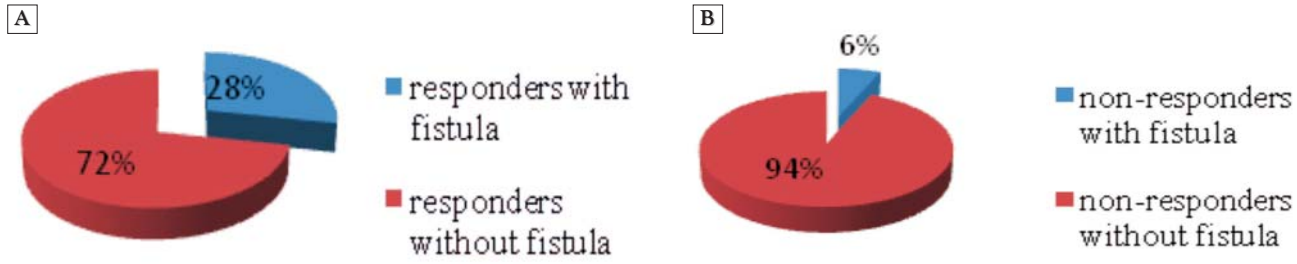

Figure 19. ***(A)*** *– Fistular complications in responders;* ***(B)*** *- Fistular complications in non-responders*

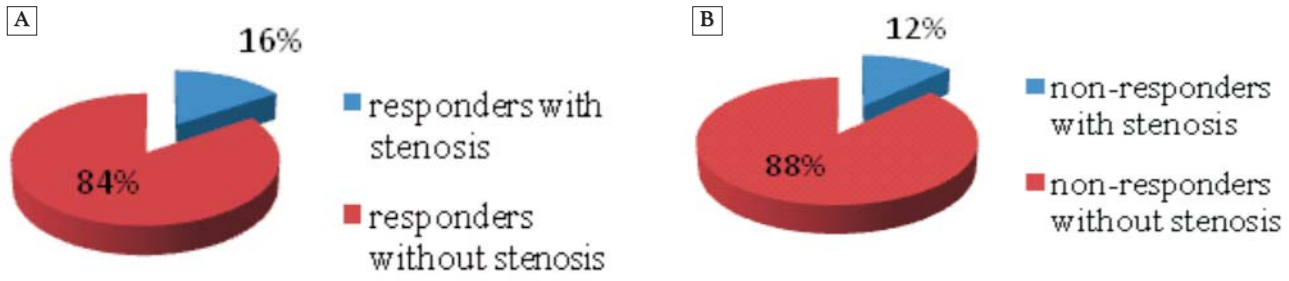

Figure 20. ***(A)*** *- Stenotic complications in responders;* ***(B)*** *- Stenotic complications in non-responders*

Stenosis and type of pathologic response to neoadjuvant RCT. Neither among the patients with neoadjuvant RCT and answered or not (RESP Yes and RESP No), we found no significant differences regarding the appearance of stenosis. Stenosis was encountered in 5 patients from the 32 with RASP Yes (16%) (*Fig. 20A*) and 2 patients of 16 with RASP No (12%) (*Fig. 20B*), differences were not statistically significant (p value = 1.000000).

Stenotic complications were met in 13.55% of surgical patients, and the complication rate was 15% for those with neoadjuvant RCT, 16% for responders and 12% for non-responders, so higher than the overall rate for those with neoadjuvant RCT and for responders, without statistically significant differences.

Another studied factor was postoperative death (mortality) in the group of 59 patients with surgery for ESC. Postoperative mortality was on the 9 deaths of 59 (15%).

Of the 48 patients we recorded 7 postoperative deaths, 3 from the group RESP Yes and 4 from the group RESP No. Although the 3 deceased from the group RASP Yes represent 9% (*Fig. 21A*), and the 4 deceased from the group RASP No represent 25% (*Fig. 21B*), we have not found that this difference is significant (p value = 0.201378).

Postoperative mortality among patients with neoadjuvant RCT is 15% (the same as the overall mortality), while among responders was 9%, lower than in non-responders (25%) and lower than the global mortality rate.

Analysis of the correlation between postoperative deaths and pulmonary complications

Pulmonary complications were encountered in 27 patients and 7 of them (26%) died post-operatively. The percentages of deaths from pulmonary complications and those who did not have this complication are not significant, but still close to the value of statistical significance p value = 0.065913.

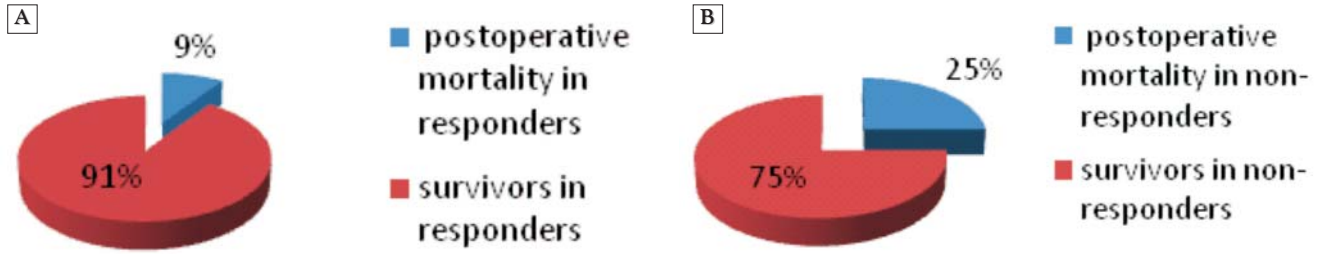

Figure 21. *(A) - Mortality rate in responders;* ***(B)*** *- Mortality rate in non-responders*

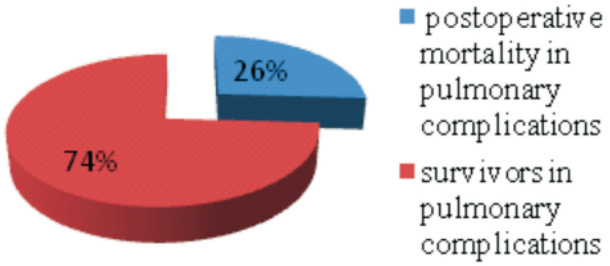

Figure 22. *Mortality among the patients with pulmonary complications*

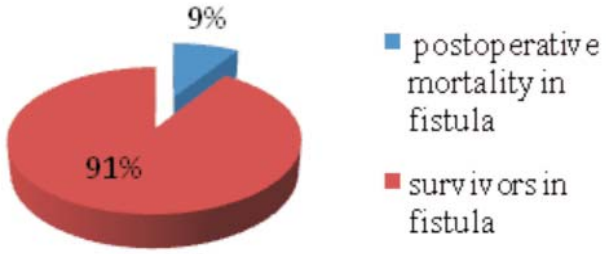

Figure 23. *Postoperative mortality of patients with anastomotic fistula*

Postoperative mortality among those who had pulmonary complications was 26% (7 of 27) (*Fig. 22*).

Analysis of correlation between postoperative deaths and fistular complications. Of the 59 surgical patients, 11 patients had anastomotic fistula. Of the 11 patients with postoperative fistula, 1 patient died (9%) and in 48 patients without fistula 8 died (17%), the difference was not statistically significant, p value > 0.05 - *Fig. 23*.

Postoperative deaths and stenotic complications

Of the 9 patients that died postoperatively, none had anastomotic stenosis, differences in percentages between postoperative deaths and those who had stenosis or not are not significant (p value=0.336621).

Long-term survival of all patients with esophageal resections for ESC with or without neoadjuvant RCT

Survival analysis was evaluated taking as reference date January 1, 2015. Overall survival at the end of the study period for the 59 patients was 11.9%, the lowest for cervical location of ESCC, and the longest (60 months - 72 months) for the medio-thoracic location - *Table 8*:

Survival analysis based on degree of nodal involvement value showed a p value close to the limit of significance (p value = 0.077). Out of the 31 surgical patients with N0 were 5 survivors and out of 28 patients with N1 were 2 survivors - *Chart 1*.

In Chart 1 we can see that the two curves preserves the "line", meaning that the N0 is always located above the N1 but the distance between them is not too high and thus we have only a p-value close to the limit of statistical significance.

Survival among patients who did neoadjuvant RCT. Overall survival among patients with neoadjuvant PCT was 14.6% and even 18.8% among responders - *Table 8*, and survival was close to statistical significance (p value = 0.072, close to 0.05).

Analyzing survival curves we have noticed that the two curves are defined, do not intersect and the distance between them is maintained and even increased with increasing duration of survival, and almost have a statistical significance - *Chart 2*.

The percentages of survivors at different intervals, for patients with response to RCT (YES) and for patients without

Table 8.

Survivors	6 months	12 months	18 months	24 months	36 months	48 months	60 months
C	71.4%	14.3%	14.3%	14.3%	Maxim 30	-	-
M	78.9%	54.4%	43.4%	40.3%	14.9%	14.9%	14.9%
T	78.6%	71.4%	50.0%	35.7%	14.3%	7.1%	0.0%

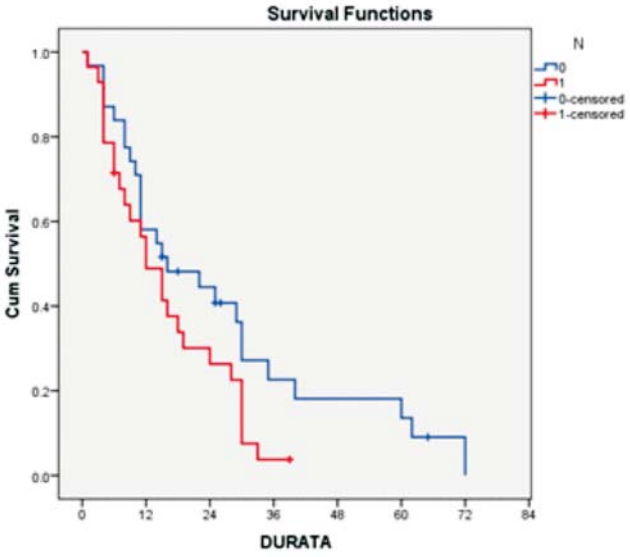

Chart 1 *Survival curve is close to be significant for N0 and N1*

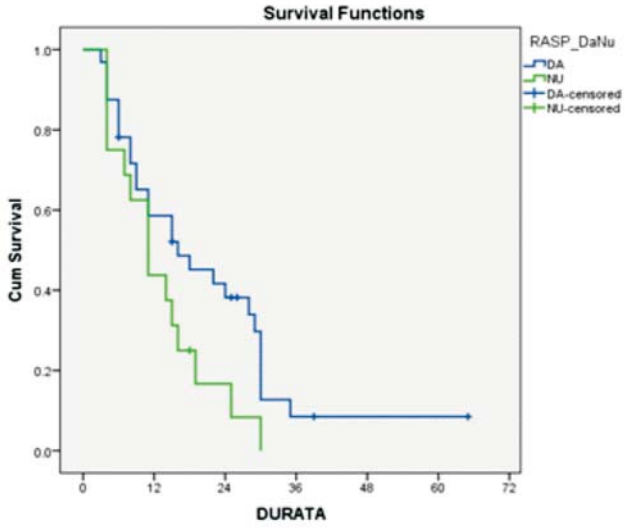

Chart 2. *Survival curves for patients with response to therapy and for patients without response, close to the value of significance*

response (NO) are shown in *Table* 9.

Survival according to imagistic response to RCT (responders - CR + PR, non-responders - NC + PD) is not significant. Overall survival of the 59 patients was 11.9%, survival among patients with neoadjuvant RCT was 14.6%, and among these, responders had a survival (18.8%) better than non-responders (6.3%), and at 60 months there were 8.5% survivors among responders and none among non-responders. Patients with neoadjuvant RCT did not have a statistically significantly better survival than those without RCT, p value > 0.05. Survival among responders is not statistically significantly higher than among non-responders, although it is close to significance (p value = 0.072)

The maximum length of survival exceeded 60 months for patients who have received neoadjuvant RCT registering 5.7%, while those without RCT reached a maximum survival of 40 months and there were no survivors at 60 months.

Survival analysis in patinets with various complications

Survival in patients with pulmonary complications (11.1%) is comparable to the survival of those without pulmonary complications (12.5%), the difference is not significant, p value = 0.099.

Survival of patients with fistula (mainly cervical fistula) was 9.1% and in patients without fistula was 12.5%, the difference was not statistically significant, p value> 0.05.

Regarding anastomotic stenosis, comparing survival in these patients with survival of those who did not develop this complication, we found that from the first category we had no survivors at the end of the study period - 1 January 2015, while in the second category we had 7 survivors, the difference was not significant, p value> 0.05.

Long-term survival of patients with esophageal resections with neoadjuvant RCT and pathologicalevaluation of the response

In the 48 patients diagnosed with ESC in General and Esophageal Surgery Clinic of St. Mary Clinical Hospital who all did neoadjuvant RCT and were all operated - total or subtotal esophagectomy and on which we have made separate survival analysis (landmark January 1, 2015), evaluation of survival according to the presence or not of pathological response to neoadjuvant RCT showed differences between the survival of pathological responders and non-responders, nearly with statistical significance (p value = 0.072, log rank test (Mantel-Cox)). Survival curves in patients with response to RCT and in patients wothout response shows that they do not intersect, and the distance between them increases with increasing duration of survival, close to statistical significance - *Chart 3*, and in responders we have recorded a survival that overcome the 60 months at 8.5% of them, while non-responders have a maximum length fo survival of 30 months - *Table 10*.

Discussion

Association radio with chemotherapy as neoadjuvant can be

Table 9.

Survivors	6 months	12 months	18 months	24 months	36 months	48 months	60 months
RCT (YES)	78.1%	58.6%	45.1%	38.2%	8.5%	8.5%	8.5%
RCT (N))	75.0%	43.8%	25.0%	16.7%	Maxim 30	-	-

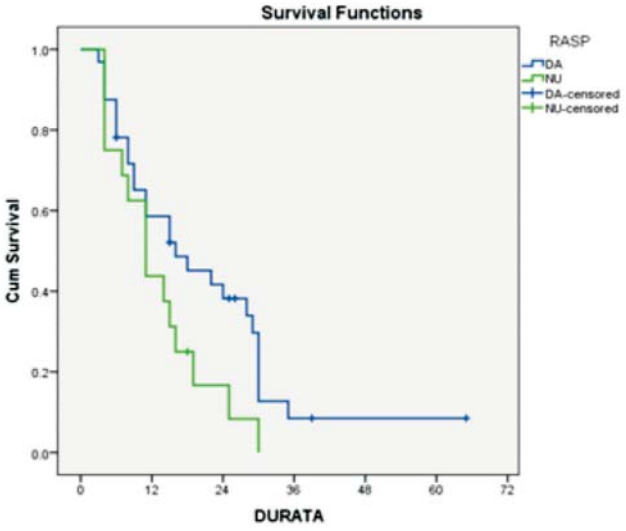

Chart 3. *Survival curves in responders and non-responders close to significance*

done in two manners (11): sequential and concurrent, we choosing concomitant therapy based on radiosensitizing effect of chemotherapy (cisplatin). Studies have shown that for ESC T3-4, N +, the effectiveness of surgery in locoregional disease control is conditioned by the possibility of occult lymphatic metastases being beyond the lymphadenectomy territory, existing in the vicinity of tumor or lymph node structures that can not be removed, making surgical resection to be often incomplete (12, 13), in these cases RCT is the therapy of first choice (14), we applied the RCT as principle for all the cases in stage 1, 2, 3.

RCT effect is expected to reduce tumor volume and to have systemic action on occult metastases (15), the therapeutic efficacy of RCT for T4, N0 is superior to surgery and prolongs survival (12), allows restaging (for responders) in case of esophagectomy (16,17). The optimal period of the end of radiochimiotherapy to surgery is 4-6 weeks, but some studies have shown even a decrease in the morbidity and recurrence when the intervention was performed 90 days after the end of RCT (18), we have performed surgery 4 weeks after the end of therapy. After neoadjuvant RCT, primary tumor and locoregional lymph node metastases (CR) sterilization meets from 12.5 to 50% of patients, depending on the aggressiveness of the protocol and stage (19), we found full imaging response in 8.3 % of patients and pathologic complete response in a smaller number of cases. This inconsistency between imaging and pathologic responses may be based on incapacity of CT (which is the main method of assessing the imaging response) to differentiate between remaining viable tumor tissue and scar tissue of fibrous reshuffling and endoscopy with biopsy can also give false negative results even in the presence of malignant tissue. Studies have shown that survival of complete responders (more than 50% at 5 years) is significantly better than those who are partial responders or those undergoing surgical treatment of first line (17). Our study detected a better survival of those who did RCT than those who did not and responders better than non-responders. Non-responder patients will be identified for palliative nonsurgical treatment having a poor prognosis and resection is rarely indicated because of the high rate of complications (20,21).

The controversy is linked to patients with complete pathologic response after neoadjuvant RCT, they should be exempt from the risks of an unnecessary major surgery. Unfortunately no clear criteria for predicting complete response to neoadjuvant RCT and often this is found on pieces of esophageal resection post RCT and another case is the absence of neoplastic infiltration of residual piece resection but the presence of lymph node residual metastases. These two contingencies recommend surgery. Some studies from literature reveal that patients with PR, NC or PD, neoadjuvant treatment exposes them to unnecessarily cytostatics toxicity and adverse effects of irradiation delaying the surgical time and increasing the risk of complications and mortality (22).

As there is not a clear and at hand (clinical, imaging) complete response prediction, the certain result is the prerogative of pathological examination of the resected piece, as mentioned above, depending on which we still apply adjuvant therapy. After assessing response to neoadjuvant therapy there are several strategies to be followed, namely:

1. Patients with complete response (CR): Opportunity of esophageal resection is questionable, lesions on esophagectomy residual pieces were missing probably if the same type of therapy had been continued provided non-existence of residual ganglion tumor that could not be evidenced by the methods of assessment of response.
2. Patients with incomplete response (PR) or no response (NC) have esophageal resection with curative character only in a small percentage of cases because they have a high risk of recurrence.

For patients with progressive disease (PD) prognosis is poor, regardless of treatment. Surgery is high risk, and neoadjuvant treatment only delays the time of surgery with increasing morbidities.

In locally advanced ESC we have two attitudes forward (Urschel):

1. Neoadjuvant RCT, followed by planned esophagectomy for cases with complete or partial response. Surgical

Table 10. *Percentage of survival in different time intervals of responders and non-responders*

Survivors	6 months	12 months	18 months	24 months	36 months	48 months	60 months
YES	78.1%	58.6%	45.1%	38.2%	8.5%	8.5%	8.5%
NO	75.0%	43.8%	25.0%	16.7%	Maxim 30	-	-

indication is maintained because there is no accurate means of differentiating between complete and incomplete response;

2. Preoperative RCT followed by selective or necessary oesophagectomy in cases of persistent disease (NC) or progressive disease (PD).

Planned esophagectomy can be changed when the progression of the disease and the general state deterioration occurs. If after the planned operation no residual tumor tissue is found on the piece is considered that neoadjuvant therapy gave best results (complete response). If after selective or necessary surgery the histopathologic result does not reveal neoplastic cells, it results in a deficiency in assessing response to RCT. The change of the planned intervention in necessity can be achieved because of side effects of RCT (nondilatable strictures, ulcers, fistulas). In planned and necessary oesophagectomies due to the RCT failure (practiced at relatively early weeks of radiation) the risk surgical is given by the magnitude of inflammation. In necessary resections practiced late after RCT (several months) due to relapse after neoadjuvant treatment, the main risk is given by the extent of fibrosis. In terms of perioperative mortality (10%) it is double than the primary interventions because of greater chance of fistular complications, respiratory distress syndrome, bronchopulmonary complications. Lack of response to neoadjuvant RCT is a negative prognostic factor in ESCC because the patient is operated under conditions where his condition is affected by subclinical radiation pneumonia and immunosuppression by affecting T cell function induced by RCT (23). Instead, intervention for relapse (done belatedly) is risky due to radiation fibrosis making the dissection difficult leading to more numerous anastomotic complications, but the prognosis is better compared to necessary oesophagectomy practiced early.

Conclusions

In our study we found the following:

1. Imaging response rate at RCT was 53% (RECIST criteria) and pathologic evaluation (MANDARD) response I found it different from the imaging (who overestimate responders).
2. Imaging response to neoadjuvant RCT showed that medio-thoracic tumors responded better than those with cervical location, the stage 2 responded better than those in stage 3.
3. Neoadjuvant RCT improves resectability and in group of the responders is significantly statistical better than the non-responders, medio-thoracic cancers resecability is better than for cervical, and the resectability post RCT is significantly statistical better for stage 2 than 3 for T2 and T3 than T4.
4. We have not found statistically significant differences between pulmonary, fistular and stenotic complications in patients with neoadjuvant RCT than those without this treatment, nor between responders and non-responders, in our study RCT did not influence the postoperative morbidity as pulmonary and fistular complications.
5. Pulmonary complications are uncommon on responders and on non-responders more common, but not statistically significant, fistula is more common in those with neoadjuvant RCT and responders, but not statistically significant, stenosis was not influenced by RCT.
6. Postoperative mortality in patients with neoadjuvant RCT is similar to the general, and for responders is lower, for non-responders is bigger than global.
7. Neoadjuvant RCT increase resectability, improves survival and maximum duration of survival more in responders than non-responders, and does not affect postoperative complications and postoperative mortality nor among the responders or non-responders.
8. In the group of patients with neoadjuvant RCT and who benefited from pathological response evaluation we found that the survival of those with pathologic response to RCT and the non pathologic responders to RCT is almost significant (p value = 0.072).

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