Neoadjuvant Radiochemotherapy for Patients with Locally Advanced Esophagogastric Junction Adenocarcinoma

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Rezumat

Radiochimioterapia neoadjuvantă la pacienții cu adenocarcinom de jonțiune esogastrică avansat local

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Radiochimioterapia (RCT) neoadjuvantă reprezintă o modalitate de management acceptată de multe centre în abordarea adenocarcinomului de joncțiune esogastrică (JEG) avansat local

Scopul: Influența RCT neoadjuvante asupra rezultatelor post-operatorii imediate și la distanță la pacienții cu adenocarcinoame de JEG avansate local.

Metoda: În Centrul de Excelență în Chirurgia Esofagiană de la Spitalul Sfânta Maria între 2010-2017 au fost tratați 62 pacienți cu adenocarcinoame de JEG avansate local. Conform clasificării Siewert și Stein lotul a cuprins tipul I – 11 pacienți, tipul II – 18 pacienți și tipul III – 33 pacienți. Radichimioterapie neoadjuvantă au efectuat 17 pacienți. Tratamentul chirurgical la cei 62 de pacienți rezecați a fost: esogastrectomie totală pe cale abdominală - 40 pacienți, esofagectomie subtotală cu rezecția micii curburi gastrice - 13 pacienți, esofagectomie subtotală prin triplu abord McKeown - 5 pacienți și esofagectomie abdomino-cervicală Orringer - 4 pacienți.

Rezultate: Morbiditatea postoperatorie a fost de 46,77% și a fost reprezentată în principal de fistule la 17 pacienți și complicații pulmonare de tipul pleureziilor, pneumoniilor și sindromului de detresă respiratorie la 12 pacienți. S-au constatat fistule la 15 pacienți: gradul 1 – 2 pacienți, gradul 2 -10 pacienți, gradul 3–5 pacienți. Mortalitatea postoperatorie a fost de 4.8%. (p_value = 0.017980 Fisher's Exact Test). Regresia stadiului inițial s-a întâlnit

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la 7 pacienți. Nu am întâlnit diferențe semnificativ statistice în ceea ce privește supraviețuirea la distanță.

Concluzii: RCT neoadjuvantă nu a avut un impact asupra morbidității postoperatorii, dar a influențat semnificativ statistic mortalitatea postoperatorie.

Cuvinte cheie: radiochimioterapie neoadjuvantă, adenocarcinom de joncțiune

Abstract

Scope: neoadjuvant RCT influence on early and long term postoperative outcomes in patients with locally advanced esophagogastric junction adenocarcinomas.

Materials and Method: Sixty two patients with locally advanced esophagogastric junction adenocarcinomas were treated at the Center of Excellence in Esophageal Surgery at St. Mary Hospital between 2010-2017. According to the Siewert classification, the group comprised of type I - 11 patients, type II - 18 patients and type III - 33 patients. Only 17 patients received preoperative RCT. The surgical treatment for the 62 resected patients was: abdominal extended gastrectomy - 40 patients, Ivor-Lewis - 13 patients, McKeown esophagogastrectomy (3 incisions) - 5 patients and transhiatal esophagectomy - 4 patients.

Results: Postoperative morbidity was 46.77% and was mainly represented by fistulas in 17 patients and pulmonary complications such as pleurisy, pneumonia and ARDS in 12 patients. Fistula occurred in 15 cases: grade 1 - 2 patients, grade 2 - 10 patients, grade 3 - 5 patients. Postoperative mortality was 4.8% ($p_{\text{value}} = 0.017980$ Fisher's Exact Test). Downstaging was observed in 7 patients. I did not encounter statistically significant differences in long term survival.

Conclusions: Neoadjuvant RCT had no impact on postoperative morbidity, but statistically influenced postoperative mortality.

Key words: neoadjuvant radiochemotherapy, esophagogastric adenocarcinoma

Introduction

Adenocarcinomas of esophageal junction have an increasing incidence lately, especially in western countries and unlike Asia, in these countries the presentation is delayed and usually it's in an advanced stage. Currently, there is no consensus regarding the management of patients with advanced local esophagogastric junction adenocarcinomas. If there is unanimity for Siewert I tumors regarding surgical technique, for Siewert II and III tumors there is still a matter of debate regarding surgical approach, operative risks that may occur and the postoperative complications (1).

An important factor to be taken into account after junction adenocarcinomas surgery is the risk of fistula (somewhere between 10-15%) and the complications that may occur with it (2,3).

Between 1996 and 2013, there have been numerous studies of chemotherapy or chemotherapy associated with preoperative radiotherapy, which concluded that neoadjuvant radiochemotherapy (and even chemotherapy alone) leads to a better postoperative outcome and longer survival for patients with advanced tumor stage comparative with surgical treatment only. According to several studies, neoadjuvant RCT can act on both microadenopathies and primary tumors, increasing the chance of complete resection and, in some cases, achieving a complete pathological response (4,5).

Materials and Method

A retrospective study was conducted on a group of 62 patients with locally advanced

esophagogastric junction adenocarcinomas that received surgery at St. Mary Clinical Hospital in Bucharest, at the Center of Excellence in Esophageal Surgery, between January 2010 and December 2017.

The group consisted of 45 men and 17 women with average age of 64. These were assessed using common investigation methods such as oesophagogastroduodenoscopy (OGD) with biopsy, barium meal, ultrasound and computerized tomography, but endoscopic ultrasound (EUS) and PET-CT were also used for a limited number of patients. The pre-operative allocation into Siewert classification was based mainly on the correlation of the endoscopic location of tumor with the radiological aspect (*Fig.1*).

According to the Siewert classification, the group comprised of type I - 11 patients, type II - 18 patients and type III - 33 patients. Neoadjuvant RCT was indicated for 17 patients.

The proposed preoperative treatment was radiotherapy 41.4-50.4 Gy (1.8-2.0Gy/d) with concurrent chemotherapy (fluoropyrimidines and oxaliplatin usual regimen, modified or adjusted in case of toxicity). The gross target volume included the regional lymph nodes identified at CT together with the clinical target volume (CTV) which is the primary tumor plus 3-4 cm superior and inferior and 1 cm lateral.

After preoperative treatment, the patients

were endoscopically, tomographically and radiologically assessed regarding response to treatment (*Fig. 2*).

The surgical treatment of these patients was, depending on the location of the tumor, according to the Siewert classification, by subtotal esophagectomy with lymphadenectomy on 1,2 or 3 fields. The technique applied to the 62 patients was: abdominal extended gastrectomy in 40 patients, subtotal esophagectomy with resection of lesser curvature - Ivor Lewis procedure in 13 patients, esophagectomy - McKeown approach (3 incisions) in 5 patients and transhiatal esophagectomy (Orringer procedure) in 4 patients.

The abdominal approach of Siewert type III tumors was performed by abdominal medial incision and a dissection of the lower thoracic esophagus transhiatally (Hill technique) (*Fig. 3*).

The Ivor-Lewis esophagectomy is combining the abdominal approach with the right thoracotomy and offers the possibility of a better dissection of the mediastinal lymph nodes, but at the same time it is a technique in which the anastomosis of the esophagus is placed in the thorax (*Fig. 4*).

Another technique used was abdominal, thoracic and cervical esophagectomy, the McKeown technique (3 incisions). This adds a left cervical incision for anastomosis, placing it at the cervical level, thus avoiding major

Figure 1. Siewert I esophagogastric junction adenocarcinoma - endoscopic appearance

Figure 2. Esophagogastric junction adenocarcinoma, post-RCT aspect, observe the disappearance of the macroscopic tumor

Figure 3. Excision of lower esophagus through transhiatal dissection

Figure 4. Flvor Lewis resection for esophagogastric junction adenocarcinoma, setting the esophageal resection limit

Figure 5. McKeown esophagectomy, distal resection limits

Figure 6. McKeown esophagectomy, tubulisation of stomach

complications and providing the possibility of easier treatment of the fistula.

The transhiatal approach (Orringer), which involves a medial abdominal incision and a cervical incision, has a cervical anastomosis between remaining esophagus and tubulized stomach (*Fig. 7*), this technique having the advantages of lower postoperative thoracic complications than the transthoracic approach, but cervical anastomosis presents a higher risk of fistula according to numerous studies.

Anastomoses were hand sewed in 23 patients, mainly interrupted absorbable sutures of Maxon 3-0, circular mechanical anastomoses were also performed in 39 patients, especially in the case of abdominal Hill approach, where manual anastomosis is

Figure 7. Transhiatal esophagectomy (Orringer) - tubulized stomach ready to be passed into the neck, length check

performed with high difficulty or transthoracic approach due to the vital risk of anastomotic fistula with this localization. Anastomotic

Figure 8. Thoracic anastomosis – the anvil is placed inside the esophageal lumen

Figure 9. Cervical anastomosis – esophagus on the left and stomach on the right

location was: abdominal in 40 patients, chest in 13 patients (*Fig. 8*) and cervical in 9 patients (*Fig. 9*). The anastomotic partner of the esophagus was the stomach in 21 patients and the jejunum in 41 patients.

Results

It was analyzed the influence of neoadjuvant RCT on postoperative morbidity generated by anastomotic fistula and pulmonary complications, immediate or distant mortality and postoperative histopathological criteria: pT or ypT, pN or ypN, or pTNM or ypTNM (*Table 1*).

Postoperative morbidity was 46.77% and was mainly represented by fistulas in 17 patients and pulmonary complications such as pleurisy, pneumonia or ARDS in 12 patients. Fistula was found in 15 patients: grade 1 - 2 patients, grade 2 - 10 patients, grade 3 - 5 patients.

There were no statistically significant differences between patients that received and those who did not received neoadjuvant radiotherapy in the incidence of anastomotic fistula or pulmonary complications. Also no statistically significant differences between the two groups of patients were observed in fistula incidence by reference to the 2015 Esophagectomy Complications Consensus Group (ECCG).

Postoperative mortality was 4.8% - 3 patients died in the neoadjuvant RCT group one due to lung complications, one of sepsis following a grade 3 fistula and one by decompensated hepatic cirrhosis in postoperative day 3.

Data processing revealed a statistically significant difference in postoperative mortality in the two groups of patients. Neoadjuvant RCT significantly influenced postoperative mortality.

All patients in the batch were operated and

Table 1. Correlation of Postoperative Morbidity with Neoadjuvant RCT - Statistical Data Processing

	PreRCT=Yes (N=17)	PreRCT=No (N=45)	p_value (test)
Fistula=yes	4/17 (23.5%)	13/45 (28.9%)	0.759385 (Fisher's Exact Test)
Fistula_grade			0.070003 (Likelihood Ratio)
1	0/4 (0.0%)	2/13 (15.4%)	
2	1/4 (25.0%)	9/13 (69.2%)	
3	3/4 (75.0%)	2/13 (15.4%)	
Lung complications	12/17 (70.6%)	39/45 (86.7%)	0.155311 (Fisher's Exact Test)

Table 2. Correlation of postoperative mortality with neoadjuvant RCT - Statistical data processing

	PreRCT=Yes (N=17)	PreRCT=No (N=45)	p_value (test)
Postoperative Death	3/17 (17.6%)	0/45 (4.4%)	0.017980 (Fisher's Exact Test)

the resected specimens were examined histopathologically. Microscopically features evaluated: pT, pN, pM, and ypT, ypN, ypM for patients that received neoadjuvant RCT.

We have noticed a significant difference in ratio between pT and ypT category (p_value = 0.015274, Likelihood Ratio) of the ones that received preoperative RCT and the other group who did not, as follows: for T0 category (pTNM), between those with preoperative treatment (11.8%) and those without (0.0%) - 2 patients with neoadjuvant RCT had no residual tumor; and for T2 category (pTNM) between those with preoperative treatment (35.3%) and those without (8.9%) - patients that did not received preoperative RCT had a deeper parietal tumor invasion compared with the ones that received chemoradiation. In the neoadjuvant RCT group no T4 category tumors were reported.

We found a significant difference between ypTNM stage for patients with neoadjuvant RCT and pTNM stage for patients that undergo

surgery first (p_value = 0.000117, Likelihood Ratio), as follow: stage II pTNM between preoperative RCT (40.0%) and no preoperative RCT (0.0%) - postoperative stage ypTNM showed that 7 patients with neoadjuvant RCT were found in stage I (1 patient) and II (6 patients), even though these patients had locally advanced tumors at baseline.

A statistically significant difference was also observed by comparing the number of metastatic lymph nodes between the two groups of patients (p_value = 0.004461 Mann-Whitney Test). Invaded lymph nodes found were significantly less in number following neoadjuvant RCT.

Median follow up for patients was 35,5 months. On January 1, 2018, 9 patients out of 17 patients with preoperative chemoradiation and 24 out of 45 patients without RCT, were surviving.

There was no significant difference in the statistical analysis of deceased patients.

Survival Analysis - Neoadjuvant RCT

Table 3. Correlation of pathological criteria pT, pN, pM or ypT, ypN, ypM for - statistical data processing

pTNM_T			0.015274 (Likelihood Ratio)
0	2/17 (11.8%)	0/45 (0.0%)	
1	0/17 (0.0%)	1/45 (2.2%)	
2	6/17 (35.3%)	4/45 (8.9%)	
3	9/17 (52.9%)	33/45 (73.3%)	
4	0/17 (0.0%)	4/45 (8.9%)	
4a	0/17 (0.0%)	2/45 (4.4%)	
4b	0/17 (0.0%)	1/45 (2.2%)	
pTNM_N			0.056873 (Likelihood Ratio)
0	8/17 (47.1%)	8/45 (17.8%)	
1	1/17 (5.9%)	13/45 (28.9%)	
2	2/17 (11.8%)	10/45 (22.2%)	
3	1/17 (5.9%)	5/45 (11.1%)	
3a	0/17 (0.0%)	6/45 (13.3%)	
3b	0/17 (0.0%)	3/45 (6.7%)	
pTNM_M			0.197309 (Likelihood Ratio)
0	16/17 (94.1%)	44/45 (97.8%)	
1	0/17 (0.0%)	1/45 (2.2%)	
1a	1/17 (5.9%)	0/45 (0.0%)	

Table 4. Correlation of pathological staging pTNM or ypTNM with preoperative RCT - statistical data processing

	PreRCT.=Yes (N=17)	PreRCT=No (N=45)	p_value (test)
pTNM Stage			
I	1/15 (6.7%)	0/44 (0.0%)	
II	6/15 (40.0%)	0/44 (0.0%)	
IIA	0/15 (0.0%)	5/44 (11.4%)	
IIB	1/15 (6.7%)	12/44 (27.3%)	
IIIA	2/15 (13.3%)	10/44 (22.7%)	
IIIB	4/15 (26.7%)	10/44 (22.7%)	
IIIC	0/15 (0.0%)	6/44 (13.6%)	
IV	1/15 (6.7%)	1/44 (2.3%)	0.000117 (Likelihood Ratio)

Table 5. Correlation of dissected lymph nodes and metastatic lymph nodes with neoadjuvant RCT - statistical data processing

	PreRCT=Yes (N=17)	PreRCT=No (N=45)	p_value (test)
Lymph Nodes Total	15.00±7.4475 15.5 [8.0, 20.0]	15.13±7.3345 14.0 [10.0, 18.7]	0.949642 (Independent Samples T Test)
Positive Lymph Nodes	1.75±2.2360 1.5 [0.0, 2.7]	6.27±7.1799 4.0 [1.0, 9.7]	0.004461 (Mann-Whitney Test)

Influence on overall survival - Statistical Data Processing

Survival analysis shows similar survival curves. However, 5 years survival in patients with neoadjuvant RCT was 0% while for patients without neoadjuvant RCT 5 years survival rate was 50.9%.

a. Estimation is limited to the largest survival time if it is censored.

Overall survival comparison at 6, 12, 18, 24, 36, 48, 60 months between preoperative RCT group and no preoperative RCT group did not show statistically significant differences.

Table 6. Correlation of long term survival with neoadjuvant RCT - Statistical Data Processing

	PreRCT=Yes (N=17)	PreRCT=No (N=45)	p_value (test)
Death	8/17 (47.1%)	21/45 (46.7%)	1.000000 (Fisher's Exact Test)

Table 7. Case Processing Summary

PreRCT	Total N	N of Events	Censored (Surviving)	
			N	Percent
da	17	8	9	52.9%
nu	45	21	24	53.3%
Overall	62	29	33	53.2%

Table 8. Overall Comparisons

	Chi-Square	df	Sig. (p_value)
Log Rank (Mantel-Cox)	.891	1	0.345
Breslow (Generalized Wilcoxon)	.557	1	0.456

Test of equality of survival distributions for the different levels of Preirad

Figure 10. Kaplan Meier survival curves test by neoadjuvant RCT(yes or no)

Discussions

Despite the increased incidence of gastro-esophageal junction adenocarcinoma in western countries (6), the optimal therapeutic protocol for locally advanced disease remains controversial. There is a poor outcome with surgery as the only therapeutic way. Multimodal therapy improves survival, but there is a lack of consensus regarding clinical approach throughout the world.

Many literature data suggest that preoperative chemotherapy or chemoradiation offers better results compared to surgery alone

for esophagogastric junction adenocarcinoma (7,8). Patients with locally advanced tumors benefit from neoadjuvant therapy compared to surgery only (9).

Neoadjuvant chemotherapy is better tolerated than adjuvant therapy and therefore dose level established is likely to be maintained in a higher number of patients. Also, neoadjuvant treatment can induce tumor downstaging, raising the possibility of complete surgical resection. This may be particularly important in western populations because these patients often have more advanced tumors than Asian patients (10).

Despite adequate resection, a significant number of patients with esophagogastric adenocarcinoma relapse locally (11). Preoperative chemoradiation can reduce local recurrences and improve overall pathological response rates, a variable associated with improved survival (11-13).

Because many patients after esophagogastric resection fail to recover to the point of tolerability for postoperative therapy, chemoradiotherapy for esophagogastric junction tumors is rarely applied (14,15).

In the studied group 17 of the patients included received neoadjuvant RCT, the remaining patients had surgery first, the complementary treatment being indicated in accordance with the histopathological criteria of the resection specimen. The neoadjuvant RCT at the dose of 45-50.4 Gy in 25-28

Table 9. Means and Medians for Survival Time

Preop RCT	Meana				Median			
	Estimate	Std. Error	95% Confidence Interval		Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Yes	32.015	4.932	22.349	41.681	32.000	7.067	18.148	45.852
No	55.798	5.729	44.570	67.026	64.000	13.069	38.386	89.614
Overall	53.143	5.067	43.213	63.074	58.000	12.128	34.229	81.771

Table 10.

Survival	6 months	12 months	18 months	24 months	36 months	48 months	60 months
PreRCT=Yes	94.1%	74.3%	67.6%	52.6%	42.0%	42.0%	-
PreRCT=No	91.0%	77.3%	72.3%	72.3%	64.3%	58.1%	50.9%

fractions was commonly the recommended dose for the control of microscopic disease.

Postoperative morbidity was 40% compared to the literature that revealed lower morbidity (around 17.9%). In the group with neoadjuvant RCT, there was no statistically significant difference in postoperative morbidity. RCT did not influence the occurrence of anastomotic fistula or its severity, nor the pulmonary complications, comparable to some published studies (16).

Tumor regression was noticed in 7 patients after initial chemoradiation and increased numbers of T1-T2 tumors in the group compared with the monotherapy group (41% vs. 0%) compared to other literature data. (17)

Radiochemotherapy significantly improved complete pathological response rate (17%) compared to other studies (15.6% versus 2.0%, $p = 0.03$, respectively, 29% complete pathological response rate) and significantly decreased the number of metastatic lymph nodes ($p = 0.004$), also supported by other literature studies (17,18).

Mortality was 4.8% similar to other literature data. All patients in the neoadjuvant RCT lot determined a statistically significant difference in postoperative mortality, unlike some literature data showing that neoadjuvant RCT did not influence postoperative mortality (16).

There was no statistically significant difference in the long-term survival curves among the lot of patients with neoadjuvant RCT versus those who did not received RCT.

Similar data are reported by Urba et al. (19) who did not notice any survival advantage in preoperative radiochemotherapy patients, probably due to insufficient statistical power. A larger Australian Phase III study ($n = 265$), which included gastroesophageal junction tumors, reported a significantly better rate of R0 resection after radiochemotherapy (80% vs. 59%, $p = .0002$), but without improvement of overall survival or disease free survival (20).

In contrast to our results, many literature data suggest that mean global survival was significantly higher in those with RCT and surgery than in the surgical only group (49.4 months vs. 24.0 months). The results were

better for preoperative RCT and surgery for 3 year survival (47.4% vs. 2.7%) (21).

Walsh et al. showed a net improvement in survival after multimodal therapy (global survival at 3 years of 32% vs. 6%, $p = .01$)

An justification for the results obtained may be the small number of patients included in the study group and the fact that patients who did not received neoadjuvant RCT followed a postoperative treatment, unlike other study groups where surgery was the only therapy.

We strongly agree with literature data that patients who underwent an esophagogastrectomy resection and have lymph node metastases on the resection specimen require some form of adjuvant treatment (22).

There are authors who consider that patients with esophagogastric junction adenocarcinomas are more susceptible to develop distant disease and therefore a systemic approach to chemotherapy can be more beneficial than an localized only treatment strategy for these patients (23).

Long-term follow-up of esophagogastric junction adenocarcinoma patients validate the overall survival benefits of neoadjuvant chemoradiotherapy. This improvement is clinically relevant for both squamous carcinoma and adenocarcinoma subtypes (24,25).

Neoadjuvant radiochemotherapy can lead to tumor regression, decreased incidence of local recurrence, and improved overall survival of patients. A therapeutic strategy that includes neoadjuvant radiochemotherapy should be implemented in clinical practice for the treatment of locally advanced esophagogastric junction adenocarcinomas (26,27).

Conclusions

Neoadjuvant RCT did not statistically influence postoperative morbidity as opposed to postoperative mortality.

Preoperative treatment RCT determined regression of the cT and cN criteria and the cTNM stage. Overall survival of patients with neoadjuvant RCT was similar with that of patients with surgical treatment and postoperative adjuvant chemotherapy.

Authors' Contributions

All authors has equal contributions.

Conflict of Interests

The authors declare no conflict of interests.

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