

# Evaluation of Neoadjuvant Radiochemotherapy Response (RCT) in Squamous Esophageal Cancer (ESC) and Implications in Therapeutic Conduct

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## Rezumat

### *Evaluarea răspunsului la radiochimioterapia neoadjuvantă (RCT) în cancerul esofagian scuamos (ESC) și implicațiile în conduita terapeutică*

Abordarea multidisciplinară a ESC s-a impus ca urmare a eforturilor de maximizare a rezultatului tratamentului acestei afecțiuni. Abordul chirurgical ca unică opțiune terapeutică nu este urmat întotdeauna de o supraviețuire la distanță foarte bună. Tratamentul concomitent radio-chimioterapic neoadjuvant al ESC poate determina la unii pacienți răspuns favorabil reducând dimensiunea tumorii, și gradul afectării ganglionare crescând rezecabilitatea și rata rezecțiilor R0, îmbunătățind prognosticul. Pentru pacienții care nu răspund sau boala progresează sub tratament RCT se întârzie momentul chirurgical, se adaugă efectele adverse ale radiochimioterapiei și crește morbiditatea și mortalitatea postoperatorie. Metodele imagistice de evaluare a răspunsului au valoare limitată doar răspunsul metabolic prin FDG-PET se apropie de răspunsul patologic. Determinarea gradului de răspuns are o importanță

mare pentru stabilirea conduitei chirurgicale de urmat: intervenție chirurgicală planificată, de necesitate sau terapie paleativă non-chirurgicală.

**Cuvinte cheie:** radiochimioterapie neoadjuvantă, răspuns, cancer esofagian scuamos

## Abstract

The multidisciplinary approach in ESC emerged as a result of efforts to maximize the treatment outcome of this disease. Surgical approach – as the only therapeutic option – is not always followed by a good distance survival. A concomitant neoadjuvant radiochemotherapy in ESC may result in a favourable outcome for responding patients, reducing the size of the tumor and the degree of lymph node damage increasing resectability and the R0 resection rate, improving prognosis. For non-responding patients or if the disease continues to progress under RCT therapy, the surgical time is delayed, adverse effects of radiochemotherapy are added and post-operative morbidity and mortality are increased. The imaging methods for the assessment of response have only limited value and metabolic response; only FDG-PET manages to come close to pathological response. Determining the response degree is very important for the establishment of the surgical conduct: planned or necessity surgery, or non-surgical palliative therapy.

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**Key words:** neoadjuvant radiochemotherapy, response, esophageal squamous cancer

## Introduction

Due to the poor results obtained in terms of survival after surgery, multimodal therapy in the treatment of ESC came into prominence as the only method of treatment of this disease. Studies have proven the beneficial role of concomitant radiotherapy and chemotherapy as neoadjuvant treatment of ESC and is based on the ability of chemotherapy to increase sensitivity to irradiation in order to improve local control of the disease (induction chemotherapy associated with irradiation) and distance involvement (lymph node disease- chemotherapy). This favorable response to RCT is obtained only in a limited number of cases; in these cases the resectability is increased by reducing tumor mass, increases the chance of R0 resections and improves prognosis. In cases that do not get a favorable response, RCT delays surgery, increases the rate of necessity interventions and increases the morbidity and mortality rates, obscuring the prognosis. Hence the important role in assessing the response and this study aims to establish imagistic and pathologic methods for assessing the response and the implications in therapeutical conduct.

### *Neoadjuvant chemotherapy in squamous cell esophageal cancer*

Cancer is essentially the uncontrolled growth in the number of cells associated with invasiveness, and the metastasis ability is the result of the interaction between genetic susceptibility and the aggression factors. The most chemotherapeutic agents affect cell mitosis and the target is on cells that have an increased rate of division, called cytotoxic effect, while others induce cell apoptosis (cell death programming). Tumors with a high growth rate and the aggressive tumors are theoretically more sensitive to chemotherapy because at any time there is a larger number of cell divisions in the cell population, consequently a bigger target. Also anticancer drugs are more effective in well-differentiated tumors because they still have regulatory mechanisms of cell growth. With the increasing number of tumor cells and mitosis, the cell differentiation is lost and growth becomes chaotic and tumors become less responsive to chemotherapy, also because the cytostatic penetration in the tumor depth is difficult in solid tumors, and multidisciplinary approach is needed for the improvement of the therapeutic effects (a combination of chemotherapy, radiotherapy and surgery). In time, a resistance to chemotherapy mechanism developed and recent research highlighted a pump (a glycoprotein) on the cell membrane responsible for removing the chemotherapeutic agent from the inside of the cell; there are drugs that inhibit the functioning of this pump, increasing the effectiveness of cytostatics. The neoadjuvant chemotherapy in

ESC addresses the primary tumor and the regional lymph; the studies reveal an improvement in survival compared with surgery as the only treatment option (1).

### *Radiotherapy in esophageal squamous cell cancer*

The mechanism of action is represented by the cancer cell DNA lesions produced by the charged particle or photon energy, directly or indirectly (through the formation of free radicals). Because tumor cells have their own mechanisms for repairing the lesions in a chain, these techniques are targeting damage to both chains by producing cellular apoptosis. Cancer cells usually have a lower differential capacity with a lower repairing capacity of sub-lethal lesions compared with the healthy, well differentiated cells. Lesions to a single DNA chain produce changes that are accumulating by cell division causing cell death or slowing their multiplication. One of the major deficiencies of photon radiotherapy is that solid tumor cells become oxygen deficient. The oxygen increases radiosensitivity by increasing the rate with which free radicals are forming. Tumor cells in hypoxic environment are 2-3 times more resistant to apoptosis. Direct damage to tumor cells by direct transfer of energy is independent of oxygenation status because these particles (protons, carbon) produce the destruction of both arms of the DNA. Some studies have shown that radiotherapy as the only treatment method in resectable ESC has a similar survival rate as in cases in which surgery was the only treatment option (2).

### *Concomitant preoperative radiochemotherapy*

Concomitant preoperative radiochemotherapy for resectable ESC has proven a better effectiveness than separate radiotherapy and chemotherapy by increasing the irradiation effectiveness because of the radio - sensitizing effect of cytostatics (3) and in locally advanced ESC improves the local control; some studies show that it does not improve significantly on survival and the identifying of the patients with significant good response to induction radiochemotherapy identifies the group of patients that may have a favorable prognosis (4). For responsive cases, the neoadjuvant RCT increases the complete resection rate by improving the staging, improves lymph node status, but unresponsive cases which require surgery have a more negative evolution than those operated per primam (5).

### *The response to radiochemotherapy in esophageal squamous cancer*

There is no universally accepted unitary classification regarding the response to radiochemotherapy and usual methods of assessment – radiological, endoscopic, endoscopic ultrasonography and computed tomography; these methods only have a limited value. The pre-therapy radiochemotherapy for ESC and esophageal adenocarcinoma (AC) reveals a similar response rate for the two histological types of esophageal tumors. Radiotherapy alone with complete

response requires for AC a higher dose of irradiation compared with ESC. By associating chemotherapy to radiation the differences in terms of complete response rate between AC and ESC are reduced compared with radiotherapy alone but with increasing the radiochemotherapy dosage for AC but the differences are smaller than for irradiation alone. However, for esophageal tumors which respond to therapy, the increasing of the response rate obtained by increasing the radiochemotherapy dose is obtained faster for AC than for ESC (6).

### **Methods for assessing the response to RCT**

To assess the clinical response to chemoradiation therapy the data used are provided by radiological examinations (X rays-barium passage), upper gastrointestinal endoscopy with biopsy (endobiopsy), endoscopic ultrasonography (EUS), computed tomography (CT) and positron emission tomography (PET/CT) – obtained before and after treatment. Unfortunately FDG-PET examination is not entered in routine practice although assessing the response value approaches the value of pathological response obtained by studying esophageal resection parts (7). The evaluation of the response by endoscopic examination and re-biopsy is relatively easy and accessible; few complications were reported but, unfortunately, response assessing value is also low. Thus it was reported that only in about 50% of the cases with negative re-biopsy (treated as a complete clinical response to radiochemotherapy), histopathology confirmed the absence of tumor cells on resection pieces. Assessment of response by endoscopic and EUS exams are based on macroscopic appearance of tumor and tomographic evaluation of response is done by measuring the maximum tumor size (maximum tumor length) and maximum tumor thickness. FDG-PET using fluodeoxyglucose is to visualize tumor tissue glucose utilization with a value close to histopathological examination of resection specimen for assessing pathological response after RCT. FDG-PET has a high accuracy for the classification of the primary tumor, regional lymph node status and distant metastasis. EDS, EUS, CT cannot differentiate between viable tumor cells and inflammatory reactions, edema and scar tissue injuries post RCT. Decreased metabolic activity in tumor tissue after irradiation is faithfully revealed by histopathological data as opposed to data from the clinical evaluations because the inflammatory changes associated with tissue edema mask the loss of tumor mass, there is the hypothesis that RCT induced tissue changes precede changes in tumor size (8). There are various methods for appreciating the response to therapy:

### **Clinical evaluation after neoadjuvant RCT**

Clinical evaluation after neoadjuvant RCT involves the improving or not of the dysphagia, assessing the weight curve evolution, the emergence of new signs and symptoms - cough, bitonal voice (signs of evolution and non response to RCT) (9).

### **Imagistic response to RCT**

(According to Guidelines for Clinical and Pathologic with Studies on Carcinoma of the Esophagus, 9 th. Ed. 24) is determined based on assessments made 4 weeks before and after treatment by studying data obtained by video-endoscopy, CT and barium passage. Based on this response, patients were classified as responders and non-responders.

Complete response (CR) – complete disappearance of macroscopic tumor and non-occurrence of a new lesion, for at least 4 weeks postRCT;

Partial response (PR) – a decrease of more than 50% of tumor size obtained by measuring two diameters, a <30% decrease in size obtained by measuring a diameter or a increase of maximum 25% in size, without progression in secondary lesions or occurrence of new lesions for at least 4 weeks postRCT;

No Change (CN) – decrease of less than 50% in tumor size obtained by measuring two diameters, a <30% decrease in the size obtained by measuring a diameter or an increase in the size of no more than 25%, without the progression of secondary lesions or without the occurrence of new lesions for at least 4 weeks postRCT;

Progressive disease (PD) – increasing by over 25% in tumor size or progression of secondary lesions or occurrence of new lesions.

WHO classification (1981) is based on the result obtained by measuring tumor diameters and has:

Full-response (CR): complete disappearance of the disease;

Partial-response (PR): at least 50% decrease in tumor mass without the appearance of new lesions. Tumor mass is defined as the sum of the tumor areas measured two-dimensionally (largest diameter (LD) x the largest perpendicular diameter) + sum of the largest diameters measured dimensional compared with reference values obtained before treatment;

No response (NC): decrease by less than 50% or an increase of more than 25% in tumor areas of one or more measurable lesions;

Progressive disease (PD): increase by at least 25% of the tumor mass or the appearance of at least one new lesion; there are the possible following situations:

- PD1: An increase of at least 25% of tumor volume with reference to the smallest similar value recorded at the beginning of treatment;
- PD 2: an increase of at least 25% of the tumor area in at least one measurable axis with reference to the lowest similar value recorded before treatment;
- PD 3: the appearance of at least one new lesion;

WHO Classification (1981) criteria was replaced by other criteria, grouped under the name of Criteria of response in solid tumors-RECIST. These criteria are based on simplified linear measurements and the response assessment has the following results:

Full-response (CR): disappearance of all target lesions;

Partial-response (PR): 30% decrease in the largest diameter of target lesions;

Progressive disease (PD): 20% increase of the largest

diameter of target lesions;

Stable disease (SD): minimal changes that can not be assigned to any of the above;

To improve the outcomes of the method there are envisaged the completing of the examination with volumetric 3D anatomical images, dynamic contrast, molecular functional imaging. Measurable lesions are considered those lesions that can be accurately measured in at least one dimension (largest measurable diameter) which must be greater than or equal to 20 mm detected with conventional techniques or greater than or equal to 10 mm using CT spiral. Non-measurable lesions are lesions smaller than 20 mm detected by means of conventional techniques, or smaller than 10 mm with spiral CT or other non-measurable lesions (ascites, inflammatory lesions, bone lesions, etc.)

Histopathological response is achieved through a rigorous examination of the resection parts and there are several classifications trying to define the response.

Mandard Classification (10) has 5 degrees of tumor regression – the percentage of tumor cells per microscope field is assigned a prognostic value together with the nodal status (11).

- TRG 1: complete regression, the histological absence of residual tumor cells and extended fibrosis of the esophageal wall with or without granulomas, no residual cancer;
- TRG 2: rare residual malignant cells among the fibrosis tissue (below 10%);
- TRG 3: increasing of the number of tumor cells but prevailing fibrosis against cancer cells;
- TRG 4: residual tumor cells dominate fibrosis;
- TRG 5: no tumor regressions;

Mandard modified classification is handy and easier:

- Complete-response: no residual viable tumor cells;
- Subtotal response: < 10% viable tumor cells;
- Partial-response: > 10% viable residual tumor cells but < 50%;
- Minimum-response: > 50% viable tumor cells;
- No answer: absence of any regressions;

Cologne Regression Classification System is based on the quantitative assessment of the percentage of tumor vital cells versus reactive change of the residual tumor tissue:

- Grd. I: little or no regression, with more than 50% vital cells remaining;
- Grd. II: partial regression, less than 50% but more than 0% vital cells remaining;
- Grd. III: subtotal regression, 0% vital tumor cells remaining;
- Grd. IV: complete regression without vital tumor cells remaining;

Grades I and II mean minor response and grades III and IV mean major response.

Schneider et al introduced a new classification system that takes into account the node metastases

- Minor histomorphological regression (degrees. I / II) with lymph node metastases (ypN1);
- Minor histomorphological regression (degrees. I/II) without lymph node metastasis (ypN0);

- Major histomorphological regression (degrees. III.A) with lymph node metastases (ypN1);
- Major histomorphological regression (degrees. III / IV) without lymph node metastasis (ypN0);

Another classification includes the following degrees of pathological tumor regression:

- Grade 3 (G3): complete disappearance of tumor cells;
- Grade 2 (G2): disappearance of more than 2/3 of the tumor cells;
- Grade 1b (g1b): disappearance more than 1/3 but less than 2/3 of tumor cells;
- Grade 1a (G1a): disappearance of less than 1/3 of tumor cells;
- Grade 0 (G0): no histopathological modification;

### **Metabolic response - PERCIST - criteria**

The PET evaluation criteria (positron emission tomography) for neoadjuvant treatment response in solid tumors involves employment of one of the following groups:

- Complete metabolic -response (CMR) F -FDG complete resolution of the target tumor;
- Partial metabolic -response (PMR): reduced by at least 30 % of F -FDG in the target tumor;
- Stable metabolic disease (MDS) when it can not do including in CMR or PMR;
- Progressive metabolic disease (PMD) increase by at least 30 % of F -FDG in the target tumor or new lesions metabolically active malignant characters;

### **Therapeutic protocol**

Therapeutic protocol in combined radio-chemotherapy pre-operatively treated ESC (limited- disease, patients with Tis-T2 N0-1, M0 - who will not or do not receive surgical treatment per primam and those with locally advanced disease - T3-4, N0-1, M0 or T1-4, N0-1, M1) consist of induction therapy with 5-Fu (1000mg/m<sup>2</sup>/day) and Cisplatin (75-100 mg/ m<sup>2</sup>/day) in 4 sessions concurrently with radiotherapy 40-50.4 or 60 Gy in total dose in divided doses (12,13). Early response and prediction of treatment response is made by FDG-PET measurements at 2 weeks after the start of the neoadjuvant treatment.

The imagistic evaluation of response is done by determinations made 4 weeks before and after neoadjuvant RCT for the same type of injury.

Complete response (CR): disappearance of all measurable lesions (> = 20 mm determined by conventional techniques)

Partial response (PR) decrease > 30% measurable lesion;

Stable disease (SD): minimal changes;

Progressive disease (PD) with over 20% growth in the measurable size;

Responders Group: CR + PR;

Non-Responders Group: SD + PD;

Imagistic response is determined by studying data obtained by barium passage, videoendoscopy, EUS, CT scan before and after neoadjuvant RCT by measuring the largest tumor size for the same tumor.

### *Videoescopy*

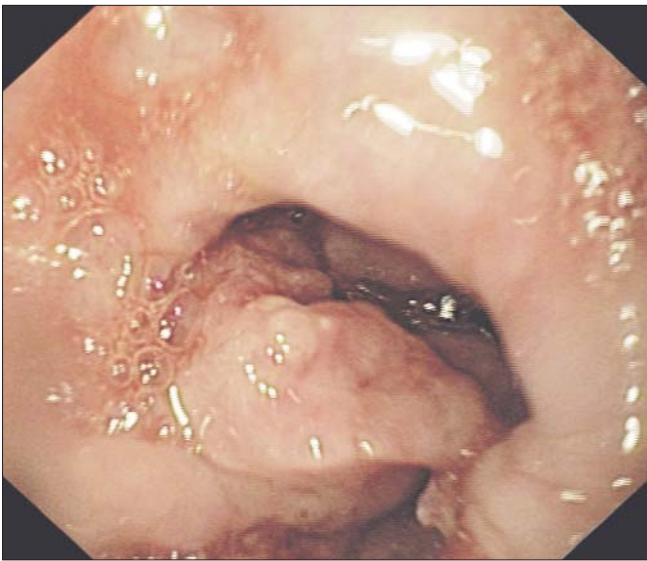
Videoscopy evaluation is made pre and post RCT for comparing the tumor size (Fig. 1, Fig. 2). The method is inadequate in assessing the degree of response (complete or incomplete) but can appreciate the presence or absence of response (14). The limit for this method is the large tumors that can not be passed with the endoscope and one can not appreciate exactly their extent; the post radiation fibrotic remoulding and necrosis prevent a proper biopsy (9).

### *Barium passage*

In assessing response to therapy, the barium passage is a simple

technique, easy to perform, handy, non-expensive and non-invasive. Barium passage is not used in general in assessing the degree of response (complete or incomplete) because volumetric determinations using conventional tumor mass are very difficult (15), but can give global information about response (presence or absence) – assessing the length of malignant esophageal stenosis pre and post RCT. It also appreciates kinetic changes or areas of stenosis without loss of safety edges (good response by fibrosis and stenosis post RCT) (9).

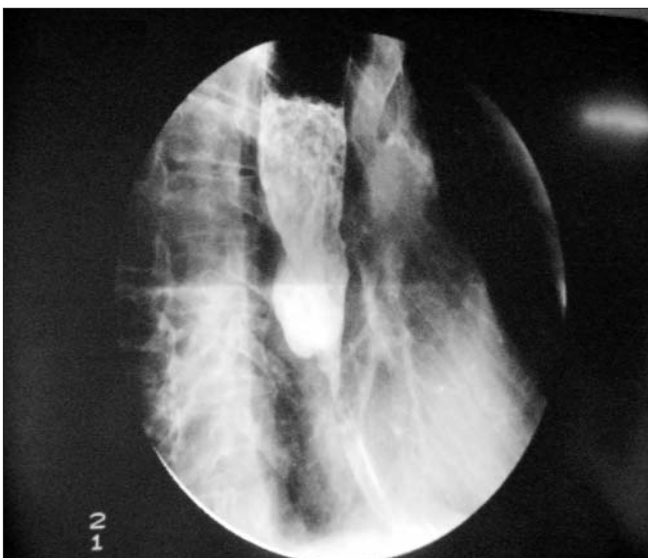
Evaluation of response by examining barium passage can show a significant reduction in the extent of tumor stenosis for the same lesions in responder group (Fig. 3, Fig. 4). In case of non - responders the radiological aspect remains unchanged or



**Figure 1.** Pre-RCT neoadjuvant chemotherapy in responders group: specifies tumor volume and tumor extent on the esophagus (for the tumors that can be passed with the endoscope)



**Figure 2.** Post- RCT neoadjuvant chemotherapy in responders group: decrease of the tumor volume and length



**Figure 3.** Pre-RCT neoadjuvant in Responders group: determine the length of tumor stenosis



**Figure 4.** Fig.4- Post- neoadjuvant RCT in Responders group: compare the length of the same malignant esophageal stenosis pre and post RCT

an increase in size of the malignant stenosis appears.

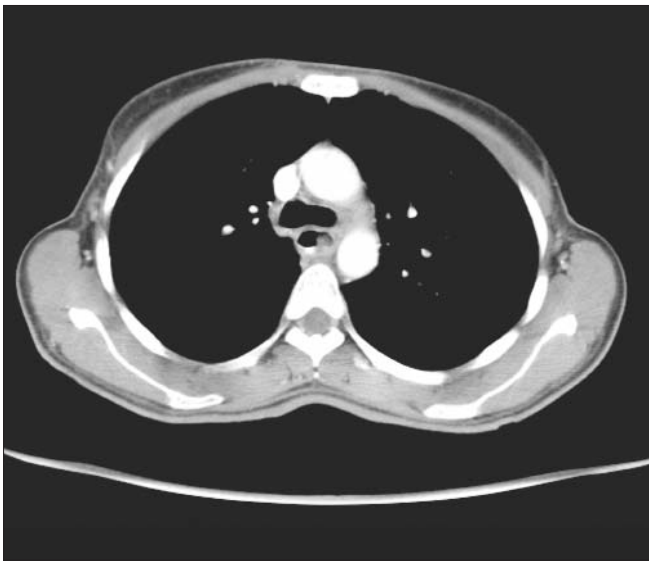
*Computed tomography*

CT is generally considered the main method for non-surgical monitoring of the response to non- surgical therapy of solid tumors. In terms of response assessment in esophageal cancer the accuracy is lower because of the difficulty of differentiating between tumor mass with viable neoplastic cells and the reactive changes (edema , fibrosis, scar tissue) (16) so that the role of CT in assessing pathologic response in ESC is low (16). Tomographic assessment of response is made by determining the maximum size of the tumor before and after neoadjuvant

RCT. The CT appearance of a tumor that has responded to treatment (responders group) is shown below (Fig. 5, Fig. 6):

*Endoscopic ultrasonography*

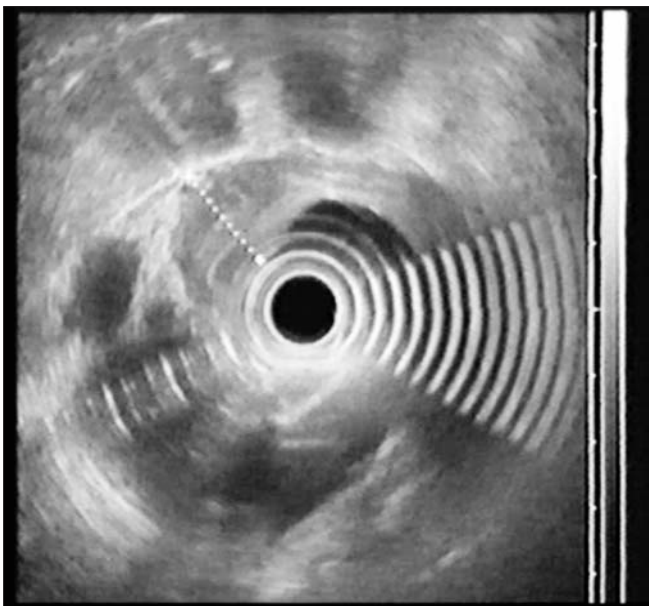
Pre and post EUS therapy permits the assessment of response by measuring the tumor size and the degree of parietal penetration, representing an important method for assessing both response and resectability (9) without being able to differentiate between complete or incomplete answer in a good response group (Fig. 7, Fig. 8). EUS has a higher value in initial staging than that of the CT, with a better differentiation between T1 and T3 (16). The limiting factors in assessing



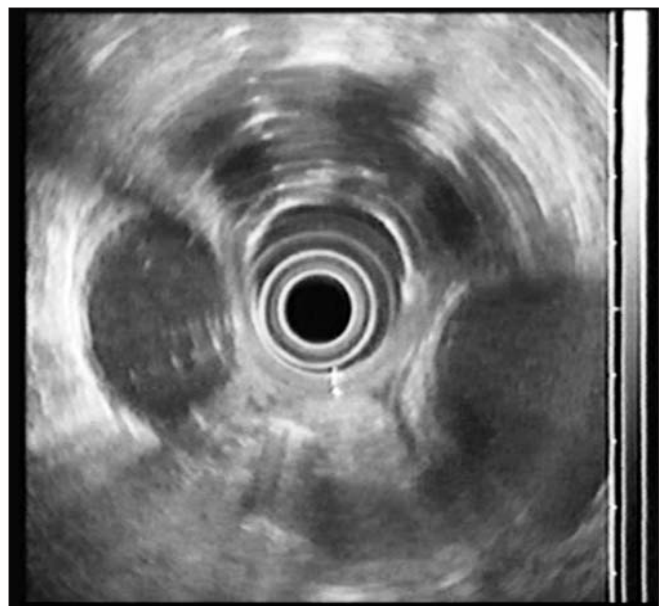
**Figure 5.** Pre neoadjuvant RCT tomography tumor evaluation (responders group)



**Figure 6.** Comparison with the Post- neoadjuvant RCT tomography tumor dimension (responders group)



**Figure 7.** EUS measuring of the tumor size after RCT (non responders group)



**Figure 8.** EUS measuring of the parietal penetration after RCT (responders group)

response are represented by radiation induced esophagitis, stenosis and compression of residual tumor lesion by the endoscope and the difficulty of differentiating residual cancerous tissue by inflammation and post radiation fibrosis (16).

#### *FDG - metabolic response assessment by PET (PERCIST criteria)*

The FDG-PET examination after neoadjuvant RCT can differentiate between viable tumor cell tissue and the necrosis scar. Inhomogeneous uptake of radiolabelled glucose by the inflammatory esophageal tissue after radio and chemotherapy and the low sensitivity of neoplastic cells after chemotherapy are limitations of the method (16). PET evaluation criteria in solid tumors (PERCIST) have been proposed as the standard method of both quantitative and metabolic evaluation of the response after radiochemotherapy treatment (17).

#### *Pathological response*

This is done by histopathological determination of the percentage of viable tumor cells of the resection specimen (modified Mandard classification):

Complete response: no tumor cells or secondary lymph node determination found on pieces of resection;

Partial response: less than 10 % viable tumor cells per examination field;

No response: more than 10 % viable tumor cells in the examination field;

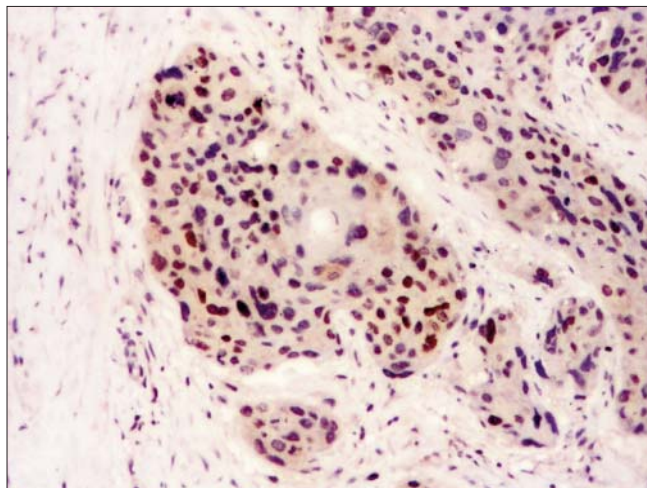
#### *Immunohistochemical aspects*

Immunohistochemical aspects in ESC with neoadjuvant RCT treatment. Overexpression of p53 in ESC, presence of c - erbB-2 and tumor proliferation marker Ki-67 are correlated with response to RCT (Fig. 9, Fig. 10 - non responders group) and are also predictors factors of response to neoadjuvant therapy (18).

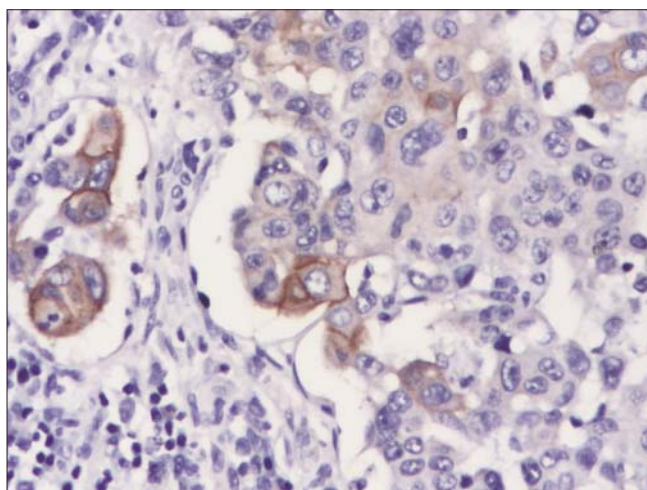
Correlation of preoperative response after neoadjuvant RCT in ESC (RECIST criteria) with pathologic response revealed by esophageal resection pieces (Mandard criteria) and with immunohistochemical aspects of preoperative primary biopsy allows the inclusion of patient in one of the groups below:

##### Complete Responders (CR):

- Macroscopic complete disappearance of the primary tumor, secondary lesions, and non-appearance of new lesions;
  - The absence of neoplastic cells on histopathological piece resection;
  - The absence of p53 expression in primary biopsy piece;
- ##### Partial Responders (PR):
- Decrease by 30% in the maximum size of the tumor;
  - Lack of progression in primary or secondary lesion size;
  - The absence of occurrence of new lesions;
  - Less than 10% of malignant tumor cells per piece



**Figure 9.** Overexpression of p53 (+) 30%, 10x (non responders group)



**Figure 10.** Presence of c-erbB-2 (+), 20x (non responders group)

resection;

- The absence of p53 expression in primary biopsy piece;  
No Chance (NC):

- Insignificant variations- dimensional minimal changes;  
- The absence of tumor progression and lack of new lesions;

- More than 10% tumor cells in resection pieces;

- Presence of c-Erb2 + p53 + in primary biopsy specimen;  
Progressive Disease (PD):

- Increase by at least 20% of the maximum size tumor numerical progression in secondary lesions, appearance of new lesions;

- More than 10% tumor cells on the resection piece;

- Presence of c-Erb2 +, P53 + in primary biopsy specimen;

## **Conclusions and Discussion**

In the responder group, RCT reduces tumor mass, decreases

the size of the primary tumor by increasing resectability and R0 resection rate and can even induce complete response, not increasing postoperative morbidity in responding patients, improves prognosis compared with primary resection for advanced ESC. In non-responders group, neoadjuvant RCT is associated with significant morbidity and mortality without improve prognosis and delays surgery without any benefit. Efforts are made to find methods for predicting the response (pathological response to RCT) to exempt those who do not respond (non-responders) of the toxic risks of cytostatics and irradiation. Prediction of response to induction therapy by endoscopy with biopsy, EUS, CT is uncertain. Making FDG-PET enables rapid adaptation and modification of therapy (scanning series, before and during the RCT, provides a good indication for metabolic response to RCT, efficacy and survival prognosis) (19).

After 14 days of starting neoadjuvant RCT, the patients are re-evaluated with PET/CT: those who respond and support a major surgery will be selected for esophagectomy. Patients who do not respond will be treated with non-surgical palliative treatment with a poor prognosis and resection is rarely indicated because of the high rate of complications (20,21).

The controversy is related to patients who develop a pathologic complete response after neoadjuvant RCT. They actually should be spared the unnecessary risks of major surgery. Unfortunately there are no clear predictive criteria of complete response to neoadjuvant RCT and most often this is found on esophageal resection pieces. Another possibility is the absence of residual neoplastic infiltration but presence of lymph node metastases on resection specimen, and the residual malignancies recommend surgery. For patients with partial or absent response and for those with progressive disease, the neoadjuvant treatment subdue to cytostatic toxicity and adverse effects of radiation. It also delays the surgical moment, losing valuable time and increasing the risk of preoperative complications and mortality, so the risk is even higher (22).

As there is no clear and convenient way (clinical imaging) to predict the complete response, the certainty result is the prerogative of the pathological examination of esophageal resection, as mentioned above, depending on which further neoadjuvant therapy should be applied.

After assessing response to neoadjuvant therapy there are several strategies that should be followed:

- Patients with complete response (CPR): For these patients the opportunity of esophageal resection is questionable after obtaining complete response, residual lesions on esophagectomy pieces would have probably been missing if the same type of therapy would have been continued, provided the inexistence of residual lymph node disease (which could not have been highlighted by the methods of assessment of response). The IHC re-examination of the resected piece is necessary for patients with complete response that had esophageal resections to exclude the presence of viable neoplastic cells.
- Patients with an incomplete, unimportant response or with persistent disease benefit from curative esophageal

resection only in a limited number of cases, due to the high risk of relapse. Preoperative morbidity and mortality are significant, and non-operated patients die following the progression of the disease.

For patients with progressive disease or absent response, the prognosis is poor regardless of treatment. The surgery involves high risk and the neoadjuvant treatment would only delay the time of surgery with increasing comorbidities.

Regarding the histopathological response according to Mandard classification patients fall into two categories: those responding - histopathological responders: TRG1 and 2 and those not responding - histopathological non-responders: TRG3,4,5. In patients with complete tumor regression surgery is not necessary and patient outcomes are good, while in patients with incomplete response, the esophageal resection followed by adjuvant treatment is discussed. Specifically, for the locoregional advanced ESC there are two treatment options:

1. Neoadjuvant RCT followed by planned esophagectomy for the cases with complete or incomplete response. Indication for surgery is preserved because there is no accurate method to differentiate between a complete and an incomplete answer.
2. Preoperative RCT followed by selective or necessary esophagectomy in case of indifferent response (persistent disease) or progressive disease (failure RCT).

Urschel makes some notable differences between planned and necessary esophagectomy:

Planned esophagectomy is formal indication and can be modified only by the progression of neoplasia and biological deterioration. If after the planned operation is not found residual tumor on resected specimen is considered the neoadjuvant therapy gave the best results (complete response). If after necessity or selective surgery histopathological results do not reveal neoplastic cells then bad assessment of response after RCT follows. This confusion can be explained by the fact that patients with persistent or recurrent dysphagia, demonstrating the continuous progress and the malignant relapse is difficult. A wall thickening evidenced by computed tomography or EUS may not be malignant but can be given by radicular sclerosis. Endoscopic biopsy can give many false negative results even in the presence of malignant tissue. The change of the planned intervention into a necessity one can be achieved because of side effects of RCT (non-expandable strictures, ulcers, fistulas).

The surgery performed after RCT presents difficulties that depend on the time period at which the intervention occurs in relation to irradiation. The extent of the side effects of radiation on mediastinal structures depends on the total dose irradiation and on the protocol. In planned and necessity esophagectomies imposed by the immediate failure of RCT (relatively early practiced after a few weeks after irradiation) surgical risk is given by the gravity of the inflammation. If necessity resections are performed late after RCT (a few months) due to relapse after neoadjuvant treatment, the main risk is given by the extent of fibrosis.

In terms of perioperative mortality (10 %), this is twice as high as for primary interventions due to the higher risk of fistulae, respiratory, and lung complications. Necessary early



esophagectomy in patients not responding to RCT have a higher morbidity than planned esophagectomy. Lack of response to neoadjuvant RCT is a negative prognostic factor for ESC because the patient is operated under conditions where is affected by subclinical radic pneumonia and immunosuppression by affecting T cell function induced by RCT (23). On the other hand, the intervention for relapse neoplasia (performed late ) is risky due to radic fibrosis that make surgical dissection difficult and can lead to more numerous anastomotic complications, but the prognosis is better compared to necessity esophagectomy performed early.

Assessing the stage efficiency of the induction RCT therapy is particularly important for the continuity of the therapeutic strategy. As mentioned above current imaging means (endoscopic biopsy, EUS, CT) do not differentiate very well between patients with CPR and those with incomplete response after induction RCT. Later, is difficult to differentiate between radic and tumorous fibrosis with imaging means but the former may hide viable neoplastic cells. The presence and intensity of lymph nodes damage diagnosed by PET does have predictive value for response to RCT. The FDG-PET series scan (before and during RCT) provides information for assessing metabolic response to RCT and survival prognosis, correctly assessing pathologic response with 71-100% sensitivity and 52-82% specificity (24,25). Response assessment by FDG-PET offers the possibility to select patients who will benefit from resection surgery (those who respond to RCT) or those who will benefit from palliative non-resection (those who do not respond) or resection therapy (a small fraction of those who do not respond - selected only on an individual basis because of the high incidence of complications and poor outcome) (26).

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