What are the criteria for full response to neoadjuvant treatment for oesophagus cancer? surgery or follow-up?

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ABSTRACT

Esophageal cancer is a progressive disease. Its survival rate is low compared to other tumors. The treatment strategy affects the survival of the patient. Treatment is controversial, especially in patients with complete response after neoadjuvant therapy. In our study, we investigated the criteria for complete response after neoadjuvant therapy and subsequent treatment processes.

Keywords: Neoadjuvant treatment, oesophagus cancer, surgery

In 2020, oesophagus cancers were reported to be the seventh most commonly seen cancer and the sixth cause of cancer-related deaths [1]. The incidence of oesophagus cancer is rising rapidly throughout the world. Although oesophagus cancers can generally be separated into two as squamous cell cancer and adenocancer, adenocarcinoma is seen at the rate of 90% [2]. The increase in oesophagus adenocarcinomas in recent years is thought to be affected by gastro-oesophageal reflux disease, Barret's oesophagus, and obesity [3]. In addition to being a cancer with an extremely aggressive course, close to 50% of patients are diagnosed when it is unresectable or metastatic. Despite a 5-year survival rate of > 85% in early oesophagus cancers, as diagnosis is generally made at an advanced stage, the 5-year survival rate is < 20% [4].

The application of preoperative and perioperative chemoradiotherapy (CRT) together with surgery has become a successful treatment strategy for gastrointestinal system malignancies in recent years. When compared with surgery alone, this treatment has been observed to increase overall survival (OS) in locally advanced oesophagus cancers. Neoadjuvant treatment methods decrease tumour volume and prolong survival by increasing R0 resection rates [5]. The degree of regression seen in the tumour after neoadjuvant treatment is extremely important in respect of disease-free survival (DFS), and the degree of tumour regression can be determined most accurately with histopathological examination by pathologists. However, as yet there is still no accepted definitive agreement or tumour response evaluation system for oesophagus cancers after neoadjuvant treatment [5].

In 2009, response criteria were defined, not only for oesophagus cancers but for all solid organ tumours. These are known as

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the RECIST criteria.

According to the RECIST criteria;

- Complete response (CR): no tumour is observed
- Partial response (PR): shrinkage of ≥ 30% in tumour size
- Progressive disease (PD): growth of ≥ 20% in tumour size
- Stable disease (SD): no change.

These response criteria are evaluated according to size using computed tomography (CT) and other imaging methods.

Evaluation of the response to neoadjuvant treatment

Although there is no clear algorithm in the evaluation of neoadjuvant response, various evaluation methods have been developed. These start with clinical evaluation together with CT, and include magnetic resonance imaging (MRI), endoscopic evaluation, biopsy, endoscopic ultrasound (EUS), positive emission tomography (PET), and histopathological grading.

Clinical Evaluation

Clinical evaluation is a method which does not present objective evidence and is insufficient in the evaluation of diagnosis response [6]. Following neoadjuvant treatment, no observation of dysphagia, the halting of weight loss, and no new symptoms (cough, hoarseness) suggest a positive response to treatment [6]. However, even if this suggests a positive response, no information is given about the degree of response.

Histopathological Response

This examination basically evaluates the relationship between the neoadjuvant response of the surgical specimen and OS and DFS. Two grading systems are at the forefront in the evaluation of response. These are the Mandard classification and the Cologne Regression Scale.

- Mandard classsification: The residual tumour is compared with the level of fibrosis formed [5].

The Mandard classification is categorised in 5 tumour regression grades (TRG).

TRG1 (pathological full response): No tumour cells. Fibrosis present in all layers

TRG2: Occasional tumour cells + fibrosis

TRG3: Many tumour cells but fibrosis is more predominant

TRG4: More cancer cells than fibrosis

TRG5: No change in regression

- Cologne Regression Scale: This evaluates changes in size from pre to post-treatment [5].

The Cologne Regression Scale is classified in 4 grades according to the response evaluation.

Grade 1: > 50% vital residual tumour cells (VTC)

Grade 2: 10-50% tumour cells

Grade 3: < 10% tumour cells (almost full response)

Grade 4: complete response

According to these classifications;

- According to the Mandard classification, TRG 4-5 are associated with a poor prognosis, and TRG1 and TRG2 with a better prognosis. This neoadjuvant response has been observed to be strongly correlated with DFS.
- According to the Cologne Regression Scale,

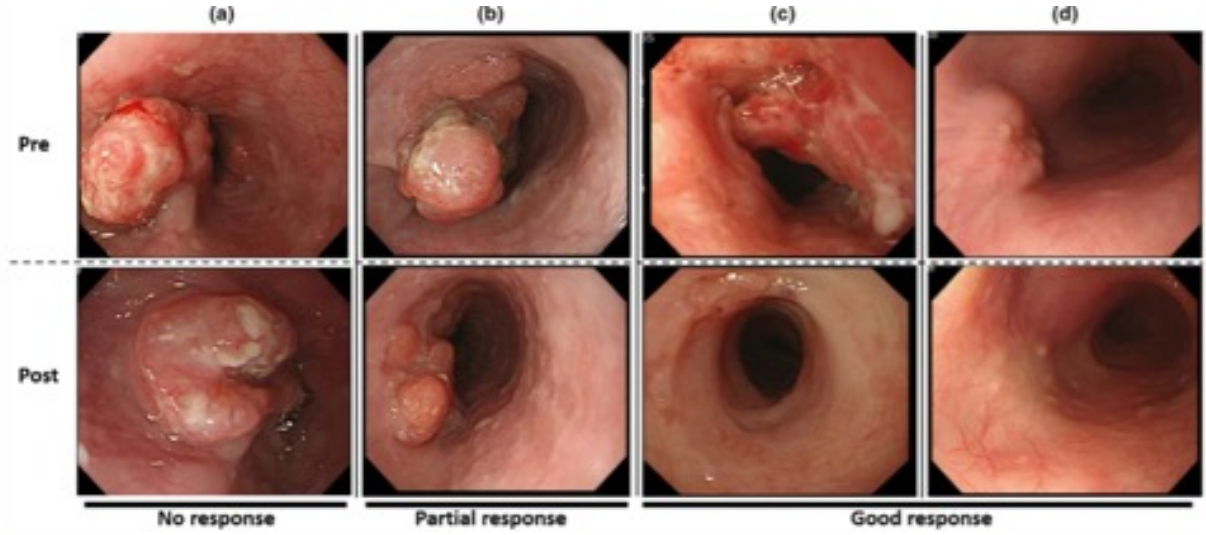

Figure 1. Endoscopic evaluation of the response to neoadjuvant treatment

patients with < 10% tumour cells, Grade 3, have a better disease prognosis [5].

Endoscopic Evaluation

Endoscopic evaluation allows macroscopic evaluation of the tumour status before and after neoadjuvant treatment.

- Endoscopic evaluation is separated into 3 categories [7]. (Figure 1)

-Endoscopic no response (eNR): No change or there is progression

-Endoscopic partial response (ePR): Despite a decrease in tumour volume, it is still present

-Endoscopic complete response (eCR): Tumour cells are not observed.

In previous studies, the prognosis has been seen to be better in patients observed with eCR and ePR. Even in patients with lymph node positivity (N1+), the prognosis and OS have been seen to be better than those of patients with no response. When the pathologies of operated patients have been evaluated, the pathological response has been observed to be correlated with the endoscopic response [7]. (Figure 1, 2)

The Japan Oesophagus Cancer Classification published by the Japanese Oesophagus Association defined evaluation criteria for the response to neoadjuvant treatment [8]. According to this classification;

- Complete response (CR): Disappearance of all target lesions
- Partial response (PR): A decrease of at least 30% in total of the largest tumour size
- Progressive disease (PD): An increase of at least 20% in total of the largest tumour size
- Stable disease (SD): No change
- According to the guidelines published by the Japanese Oesophagus Association, some criteria and findings were determined to define full response [8]. Accordingly;
- The criteria for endoscopic full response to neoadjuvant treatment [8];
- 1-The disappearance of irregular mucosa and ulcerated areas
- 2-No wounds or narrowing within the lumen
- 3-No observation of active inflammatory structures (in the form of white coating)
- 4-Negative biopsy findings
- 5-Clear visibility of the whole oesophagus
- 6-The observation of scarred areas or a smooth mother-of-pearl appearance in the oesophagus mucosa

In the evaluation of response following neoadjuvant CRT treatment, changes on the mucosa surface are evaluated with endoscopic examination. In previous studies, endoscopic evaluation has been observed to have 22-65% sensitivity and 50-85% specificity for complete response [9]. It has been recommended that biopsy is repeated after neoadjuvant treatment to increase accuracy in the evaluation of complete response [9]. In a study by Bates of endoscopic evaluation, it was reported that despite negative biopsies in 7 of 17 patients, residual cancer cells were observed [10]. Schneider repeated biopsies in 80 patients and reported sensitivity of 36% and specificity of 100% [11]. Despite these studies, the taking of biopsy has not been accepted as a rule in the endoscopic evaluation of complete response [9].

In a review of 12 studies with a total of 1281 patients, it was concluded that endoscopic biopsy has high specificity but low sensitivity. It is not surprising that endoscopic biopsy provides a high rate of false negative results because the biopsies are only taken from the superficial mucosal layer [12].

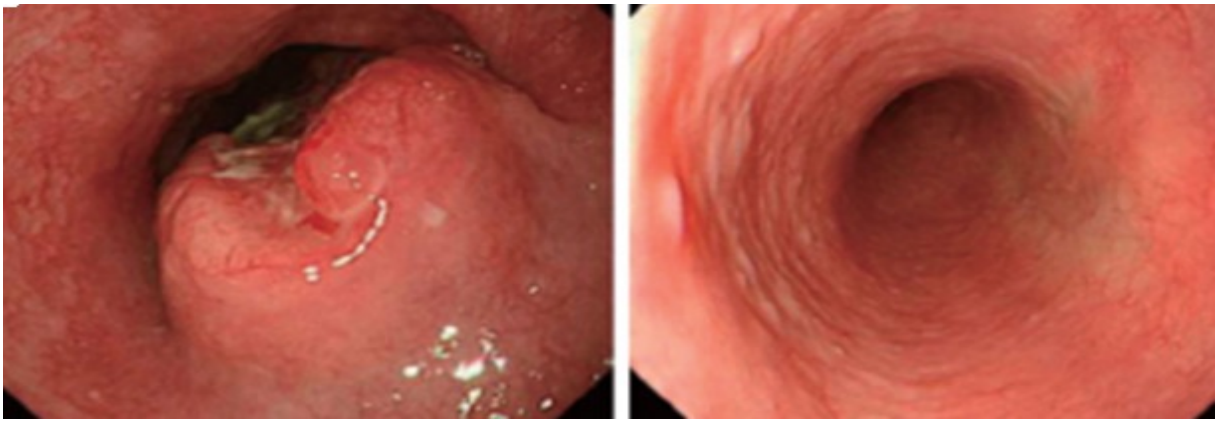

Figure 2. After neoadjuvant treatment in a patient with type 2 grade 3 oesophagus cancer before the procedure, only scar tissue was seen to remain and the patient was evaluated as complete response

In a study of 29 patients who received neoadjuvant CRT, the oesophagus wall was evaluated with biopsy taken again after the neoadjuvant CRT, and intra-epithelial lesions < 5mm in size were observed in 7 cases, and tumour nests were observed in the submucosa or m. propria in 9 cases [13].

With the deep biopsy method (bite-on-bite biopsy) an increase has been observed in recent years in the identification of submucosal residual tumour deposit. In patients with tumour negativity, 85% pCR has been observed in the surgical specimen with this method [14].

In a study by Van Rossum et al.,it was concluded that in the determination of residual oesophagus tumour in patients who had received neoadjuvant CRT, endoscopic biopsy was a specific but not absolutely sensitive method for determination [15].

Endoscopic Ultrasound (EUS) Evaluation

Tumour evaluation with EUS is frequently used, especially in oesophagus and rectum cancers. Despite the high accuracy rate of EUS in the evaluation of primary tumour depth (T) and lymph node status (N+/-), this reliability decreases after neoadjuvant treatment. The reason for this is that it remains insufficient in the evaluation of residual tissue caused by inflammation, fibrosis, oedema and scarring formed in the tissue after neoadjuvant treatment [15].

In a study of 110 patients, T-stage was evaluated again with EUS after neoadjuvant CRT, and success was observed to be low at 39% [16]. In another similar study, complete pathological response was evaluated at low rates such as 0-25% with EUS in the evaluation of response after neoadjuvant treatment [17].

In the accurate evaluation of neoadjuvant response, EUS is more successful in the evaluation of lymph node status (N stage) than of tumour depth (T stage). In the above-mentioned study of 110 patients, the N stage accuracy rate (58.2%) was seen to be higher than the T stage accuracy rate (39.1%) [16]. The N stage accuracy rate was reported as 64% and the T stage accuracy rate as 37.3% in another study of 59 patients [18].

When lymph node size is evaluated with EUS, lymph nodes > 10mm are considered malignant. In a meta-analysis of 10 studies including 602 patients, the identification of residual lymph node metastasis > 10mm was measured as 73.5% when examined with EUS, but this rate was 31.1% in lymph nodes > 5mm [15].

Biopsy obtained with EUS has not been seen to provide any additional benefit in N stage diagnosis because of nodal necrosis and inflammation in that region. Moreover, the rate of false negative biopsies has been found to be high in biopsies taken with EUS after neoadjuvant treatment [19].

It has been attempted to define complete response criteria based on wall thickness in some studies. In a study of 66 patients, a decrease of > 50% in wall thickness and < 6mm thickness were found to be significantly associated with complete pathological response. It was observed that every 1mm increase in wall thickness reduced the probability of complete response by 31.3% [12].

Ota measured tumour diameter before and after neoadjuvant CRT, and those with response were identified with 94% accuracy. Studies have shown that the most appropriate time for re-grading with EUS is 3 weeks after the completion of neoadjuvant CRT [12].

Foci of residual adenocarcinoma after neoadjuvant treatment have been observed in biopsy taken with EUS, as in endoscopy.

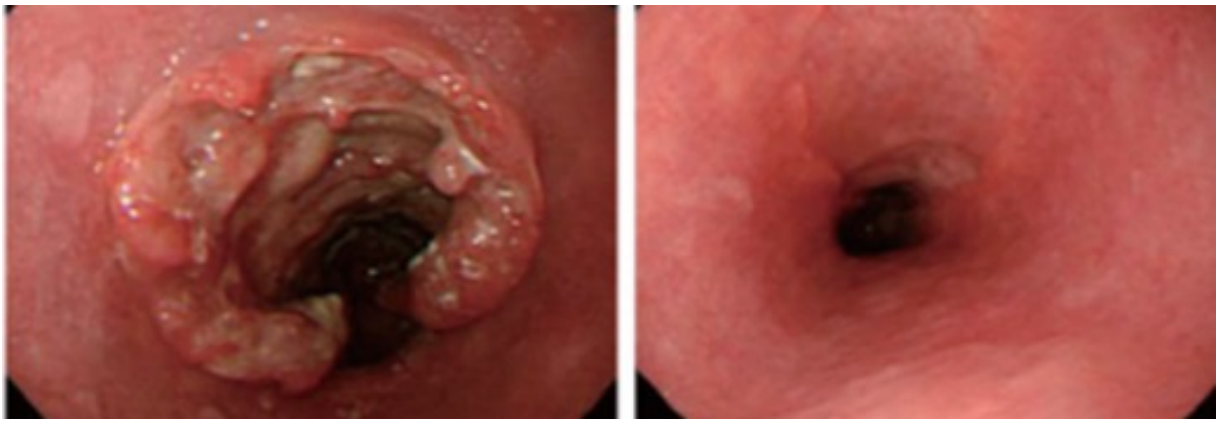

Figure 3. After neoadjuvant CRT treatment in a patient with type 2 grade 4a oesophagus cancer before the procedure, no tumour was observed in the endoscopic evaluation

Magnetic Resonance Imaging (MRI) Evaluation

In MRI evaluation, the tumour wall thickness and lymph node involvement are evaluated. MRI can evaluate the response in the early period after neoadjuvant treatment. At 10-15 days after completion of neoadjuvant treatment, the response can be evaluated with MRI [20].

Evaluation with diffusion MR has been observed to be more effective in response evaluation. Diffusion MR results are based on the information given about tissue density with contrast differences during the passage of water molecules between different tissues. The apparent diffusion coefficient (APC) is the measurement value of the free diffusion of water molecules. A high APC value shows higher diffusion. In malignancies showing a good response to treatment or in normal gastrointestinal organs the APC value is observed to be higher. Previous studies have examined APC values at 2-3 weeks after neoadjuvant treatment and have determined higher values in patients with complete response (pCR 34.6%- nonpCR 14%) [21]. In a study of 45 patients, diffusion MRI was determined to have 87% sensitivity and 58% specificity in the differentiation of good response (< 10% residual tumour cells) and poor response [20].

Computed tomography (CT) evaluation

Tumour size and oesophagus wall thickness are evaluated in evaluations made with CT imaging. In addition, metastasis and the status of lymph nodes and vascular structures can also be observed. However, CT is not a superior test in the evaluation of complete response. The accuracy rate is low in the evaluation of response in tumour cells because of the inflammation, oedema and fibrosis formed after neoadjuvant treatment. In previous studies, wall thickness of ≤ 5mm after neoadjuvant treatment is interpreted as able to show predicted complete response [22]. Perfusion CT imaging has been used in several studies in the evaluation of response to neoadjuvant CRT (23). Three perfusion parameters of blood flow (BF), blood volume (BV) and mean transit time (MTT) are used for oesophagus tissue in perfusion CT evaluation. Deng et al. reported that in 50% of patients with advanced grade oesophagus cancer who received neoadjuvant chemotherapy, BF and BV were significantly reduced and MTT increased in those with clinical response [24].

Positron Emission Tomography (PET / PET-CT) imaging evaluation

The metabolic activity of tumour cells is examined in PET evaluation. In the evaluation of metastasis and re-grading after neoadjuvant CRT, PET is extremely useful. There are a great many studies in literature showing pCR and evaluation of response with PET following neoadjuvant CRT. In those studies, a decrease in the SUVmax value has been found to be consistent with treatment response. Like the RECIST criteria, response criteria have also been defined for PET imaging. The PERCIST criteria are based on the evaluation of solid tumours with PET (25). According to these criteria;

- Complete metabolic response: Complete FDG resolution of tumour cells
- Partial metabolic response: A decrease of at least 30% FDG in tumour cells
- Stable metabolic disease: No change
- Progressive metabolic response: An increase of at least 30% FDG in tumour cells or the observation of new lesions

In a study by Wieder, a 44% decrease in the SUVmax value was found to be consistent with histopathological response (< 10% tumour cells observed in resection material) in patients with oesophageal squamous cell carcinoma who received neoadjuvant treatment [26]. In a study by Molena of patients with oesophageal squamous cell carcinoma, when the SUVmax value decreased by 70%, normal mucosa was observed in the endoscopic evaluation and no residual disease was observed in the biopsies taken, and of these patients, pathological full response was seen in 65% [27]. In another study, PET/CT was determined to have 67% sensitivity and 68% specificity in SUVmax evaluation after neoadjuvant CRT. It was attempted to determine a cutoff value for SUVmax in that study, and regression values of 30%-50%-70% were examined. All were found to be associated with 3-year OS. The strongest histopathological response was observed to be correlated with a decrease of 70% in metabolic activity [28]. Several studies have evaluated SUVmax < 4 as complete response, but a clear cutoff value has not been able to be defined [29].

In an analysis of 56 studies evaluating a total of 3625 patients, the capability of CT, PET, EUS, and MR imaging methods was examined in the evaluation of complete response. It was concluded that none of the methods provided sufficient success in showing complete response [30].

Surgery or Follow-up after Neoadjuvant Treatment?

Oesophagus cancer is a type of cancer with an extremely aggressive course. Even after surgical treatment, survival is not long. However, previous studies have shown that neoadjuvant CRT has prolonged survival. In the CROSS study, a survival benefit of 14% was observed with surgery after neoadjuvant CRT. According to the CROSS study, a pathological complete response was observed in 29% of patients (49% SCC, 23% AC) who received neoadjuvant CRT treatment. Following these high response rates, an organ-protective follow-up strategy was developed. Close follow-up is required following neoadjuvant CRT in this strategy [31]. There are great advantages to this treatment strategy, especially in respect of perioperative morbidity and mortality, and the decrease in quality of life which occurs after oesophagectomy is not observed [32].

In a study of 36 patients, in which a follow-up group was compared with a surgical group in respect of survival, no statistically significant difference was determined (58 months/51 months) [14]. In another study, when examined in respect of distant spread, the rates were observed to be similar at 31% in the follow-up group and 28% in the surgical group [33]. A study in Italy compared a follow-up group (n:38) and a surgical group (n:39) and reported similar rates of 57% in the follow-up group and 50% in the surgical group [34].

In a study that included 143 patients, surgery was applied to 43 patients following neoadjuvant CRT and definitive CRT (dCRT) to 100 patients. In respect of DFS, the rates of the surgical group were higher but the difference was not statistically significant, and no significant difference was determine between the groups in respect of OS. In the dCRT group, DFS was determined as 22.8% and OS as 17.6%. In the patients applied with dCRT+salvage surgery, the OS rates were observed to be higher than those of the patients who did not undergo surgery (35). In another study of 100 patients, the histopathological grading was calculated and pCR was observed in 45% of the patients. Survival was determined as 62.7 months in the patients with pCR and 5-year survival was found to be 58% [36].

In a study which scanned patients diagnosed with oesophagus adenocarcinoma between 2004 and 2014, patients applied with oesophagectomy were compared with those applied with neoadjuvant CRT+surgery and patients administered dCRT. Over the years there was seen to be an increase in dCRT and neoadjuvant CRT treatment methods. In the follow-up period of the patients, the best result in 5-year survival was in the patients treated with neoadjuvant CRT+surgery [37]. In an analysis of 2633 patients with grade 3 oesophagus adenocarcinoma, the 5-year survival rates were found to be dCRT 13% and neoadjuvant CRT+surgery 27%, and it was concluded that neoadjuvant CRT+surgery was statistically significant in respect of the survival benefit (38). In another meta-analysis of 4188 oesophagus adenocarcinoma patients, neoadjuvant CRT+surgery was found to be more effective in terms of survival than surgery alone [39]. In a study by Haefner, no statistically significant difference was determined between dCRT and neoadjuvant CRT + surgery in respect of 5-year survival [40]. Another study reported that of 125 patients who received neoadjuvant CRT, pathological complete response was observed in 27% [41].

A study including 130 oesophagus cancer patients examined patients treated with neoadjuvant CRT + surgery and patients treated with dCRT. Local recurrence was observed in 10.8% of the neoadjuvant CRT + surgery group and in 21.5% of the dCRT group. When evaluated in respect of survival, the period of DFS was found to be 15.6 months and OS was 20.6 months in those applied with neoadjuvant CRT, and DFS was 14.9 months and OS was 25.9 months in the patients who received dCRT. No statistically significant difference was determined between the groups in respect of these parameters [40]. In a very small study of 3 patients, surgery could not be performed in the the first patient because of the general condition, so neoadjuvant CRT was completed, and no recurrence was observed in the 4-year follow-up period. The second patient refused surgery, so neoadjuvant CRT was completed, and no local recurrence was observed in the 1-year follow-up period. In the third patient, complete response was observed but local recurrence developed in the follow-up period and the patient progressed to oesophagectomy [42].

Consequently, as there is no consensus in respect of a treatment protocol, applications are made according to the guideline recommendations.

According to the NCNN guidelines, if tumour cells are not observed in the follow-up evaluation after neoadjuvant CRT in both squamous cell carcinoma and adenocarcinoma of the oesophagus, the recommended view is that both follow-up can be applied and surgery can be performed.

According to the Japanese guidelines, endoscopy criteria have been defined in respect of complete response evaluation following neoadjuvant CRT treatment, but there is no clear consensus on a treatment

strategy.

CONCLUSION

Oesophagus cancer is a cancer which can have an extremely aggressive and mortal course. It has been attempted to prolong survival with various treatment strategies, and recently neoadjuvant treatment strategies for this purpose have become more prominent. However, there is no clear consensus about which methods can more accurately evaluate the response to neoadjuvant treatment. The survival advantage and success cannot be denied in patients with complete response after neoadjuvant CRT, but the reliability of the methods used to determine complete response to neoadjuvant treatment is not clear. No full consensus has been established on this subject.

Together with the lack of a clear answer to the question of how complete response can be evaluated, an answer is still being sought to the question of whether follow-up or surgery should be applied after neoadjuvant treatment. Two large-scale studies, the SANO study and the French ESOSTRATE study, are currently seeking an answer to this question. According to the SANO study, the follow-up strategy following neoadjuvant CRT has not produced results lower than those of the surgical strategy. The ESOSTRATE study, which includes 300 patients with oesophagus squamous cell carcinima and oesophagus adenocarcinoma, and the SANO study, which is at phase 2-3 level, are still ongoing and will be concluded in 2023 [43, 44].

Authors' Contribution

Study Conception: DD,; Study Design: DD, MAA,; Supervision: MAA,; Materials: DD,; Data Collection and/or Processing: DD,; Statistical Analysis and/or Data Interpretation: MAA,; Literature Review: MAA,; Manuscript Preparation: DD and Critical Review: MAA.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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