Review Article

Neoadjuvant treatment for advanced esophageal cancer: response assessment before surgery and how to predict response to chemoradiation before starting treatment

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Abstract: Patients with advanced esophageal cancer (T3-4, N) have a poor prognosis. Chemoradiation or chemotherapy before esophagectomy with adequate lymphadenectomy is the standard treatment for patients with resectable advanced esophageal carcinoma. However, only patients with major histopathologic response (regression to less than 10% of the primary tumor) after preoperative treatment will have a prognostic benefit of preoperative chemoradiation. Using current therapy regimens about 40% to 50% of the patients show major histopathological response. The remaining cohort does not benefit from this neoadjuvant approach but might benefit from earlier surgical resection. Therefore, it is an aim to develop tools for response prediction before starting the treatment and for early response assessment identifying responders. The current review discusses the different imaging techniques and the most recent studies about molecular markers for early response prediction. The results show that [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) has a good sensitivity but the specificity is not robust enough for routine clinical use. Newer positron emission tomography detector technology, the combination of FDG-PET with computed tomography, additional evaluation criteria and standardization of evaluation may improve the predictive value. There exist a great number of retrospective studies using molecular markers for prediction of response. Until now the clinical use is missing. But the results of first prospective studies are promising. A future perspective may be the combination of imaging technics and special molecular markers for individualized therapy. Another aspect is the response assessment after finishing neoadjuvant treatment protocol. The different clinical methods are discussed. The results show that until now no non-invasive method is valid enough to assess complete histopathological response.

Keywords: Esophageal cancer; squamous cell carcinoma; adenocarcinoma; neoadjuvant chemoradiation; response prediction; response assessment

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Introduction

Surgery remains the first-choice treatment for resectable esophageal cancer (1). Resection of early esophageal cancer (T1-2) usually results in long-term survival, but the prognosis is poor with esophagectomy alone for advanced stages (T3-4). For three decades, numerous trials have tested a variety of preoperative treatment strategies. Neoadjuvant radiochemotherapy or chemotherapy improved the overall survival of patients with advanced carcinomas of the esophagus by about 10% in 5 years according to current Cochrane analysis, meta-analysis, the actual prospective, randomized CROSS-trial and retrospective studies (2-5). However, the results of several trials with preoperative chemoradiation showed that only patients with a major

histopathologic response will have a significant survival advantage (2,6,7). In addition, some research groups discuss the necessity of surgery for patients with complete response (CR) after preoperative chemoradiation (8). Consequently, effective methods for early and late response assessment are required in order to perform these different individualised, response-guided treatment concepts.

Until now, there are several ideas for prediction of individual response to chemoradiation or chemotherapy published, e.g., endoscopy, endosonography (EUS), computed-tomography, [^{18}F]-fluorodeoxyglucose-positron emission tomography (FDG-PET) or molecular markers. The aim of this review is to summarize the actual knowledge about the possibilities of evaluation to predict response of multimodality treatment of patients with esophageal cancer.

Response prediction or response assessment

Definition of response

There is only one valid method to evaluate the response of chemoradiation of the tumor by pathologic work-up of the resected specimen. Therefore, the gold-standard of response evaluation is the histopathologic response evaluation of the primary tumor and the resected lymph nodes (9). The WHO-classification for CR was defined as complete disappearance of all known disease. Based on the response evaluation criteria in solid tumors (RECIST), the guidelines to evaluate the response to radiotherapy, chemotherapy and chemoradiotherapy for esophageal cancers are established (10). Mostly the histopathologic regression of the primary tumor after neoadjuvant therapy is divided in four or five grades. As an example the Cologne Regression Scale is classified into four categories: grade 1, CR; grade 2, nearly CR with less than 10% vital residual tumor cells (VRTCs); grade 3, 10% to 50% VRTCs; and grade 4, greater than 50% VRTCs. Because of prognostic implications, regression grades 1 and 2 were classified as major histomorphologic response compared to grades 3 and 4, which were categorized as minor histopathologic response (6,11).

In some papers, the definition of pCR is extended to freedom from tumor in the lymph nodes. Hölscher *et al*. defined a combined classification of primary tumor regression and lymph node status in three grades which represent a simple and reproducible prognostic classification of the effect of neoadjuvant treatment in esophageal adenocarcinoma (12).

Response assessment

Surgery with or without neoadjuvant therapy is the therapy for choice with the best prognosis for patients with advanced esophageal cancer, providing a macroscopically and microscopically complete resection (2). Especially patients with CR of the primary tumor without lymph node metastasis had a very good prognosis with a disease specific 5-year survival rate of 68% (13). But some patients after neoadjuvant therapy are not fit enough for an extensive surgical procedure like transthoracic esophagectomy. A further question is the necessity of such a procedure after "CR". The discussion is supported by two randomized studies comparing chemoradiation alone versus neoadjuvant chemoradiation followed by surgical therapy in patients responding to preoperative therapy (8,14). Both studies demonstrated no significantly better overall survival for patients with esophagectomy, but significantly better local disease control in the surgery group. Therefore, it could be of interest to identify the subset of patients who have achieved a major pathologic response to consider avoiding resection and on the other hand guiding the non-responders to surgical therapy. Different clinical methods for response evaluation during restaging after successful neoadjuvant therapy have been published.

Endoscopy, endosonography (EUS)

Response evaluation by endoscopy is easily performed, has very few complications, and is easily available. Lim *et al*. could demonstrate a significant prolonged disease-free survival after endoscopic CR 6 weeks after definitive chemoradiation for esophageal cancer (15). Adelstein *et al*., however, could demonstrate that endoscopic response evaluation after neoadjuvant chemoradiation had a sensitivity of 22% and a specificity of 85% only to detect pathologic CR (16). Endoscopic response evaluation is therefore by far too inaccurate to predict major histopathologic tumor regression or pathologic complete remission and is dispensable if performed for this indication. It is, therefore, important that none of the patients should be harmed by denying surgical resection if an endoscopic CR is detected.

Several groups extended response evaluation by endoscopy through taking rebiopsies to improve accuracy of response prediction. Bates *et al*. could show that in 7 of 17 (41%) patients with negative biopsies, tumor cells could still be detected in the resected specimens (17). In a larger series by Brown *et al*., 100 consecutive patients

were evaluated by endoscopic rebiopsy (18). In 30 patients, rebiopsy specimens were negative for tumor cells and classified as clinical complete responders. Histopathologic evaluation of the resected specimens could demonstrate however, that a pathologic CR was present in only 15 of 30 (50%) negative rebiopsies. The results from Schneider *et al*. with a more extensive analysis of regression show an accuracy of 47% and, therefore, compare favorably with already published studies based on pathologic complete remission (19). A positive rebiopsy is surely the secure proof for residual tumor (positive predictive value 100%). The more important negative result, however, is too inaccurate to draw any therapeutic consequences. Sarkaria *et al*. performed endoscopy with biopsy for 146 patients undergoing neoadjuvant chemoradiation for esophageal cancer (20). A total of 118 patients had no tumor in the biopsy. The prognosis of patients with negative biopsy was comparable to those patients tumor in the biopsy. Therefore, all patients with negative rebiopsies should be consequently resected after neoadjuvant therapy, and for this very reason, endoscopic rebiopsy is not recommended.

EUS for classification of the cT-category before initiation of neoadjuvant therapy is known to be valuable (21). Adelstein *et al*. could show that clinical response evaluation by EUS according to WHO criteria has a sensitivity of 17% and a specificity of 93% (16). Similar results were reported in various studies with accuracy to determine the ypT-category after neoadjuvant therapy between 37% and 85% (19,22,23). Several problems, however, were reported using EUS for response evaluation. Downstaging is frequently seen and cannot be demonstrated by histopathology (understaging), and in patients with ypT0- and ypT1-categories overstaging is frequently present (23). Ngamruengphong *et al*. performed a systematic review of published information of diagnostic accuracy of EUS after completion of neoadjuvant therapy (24). The sensitivity of EUS ranged from 20% to 100% and the specificity ranged from 36% to 100%. Restaging by EUS before resection did not accurately predict pathologic stage in patients with esophageal cancer who received neoadjuvant treatment.

PET and PET/CT

FDG-PET is a valuable technique for tumor visualization, initial staging, detection of recurrent disease and radiotherapy planning in esophageal cancer (25), being even superior to anatomic imaging modalities in its ability to detect distant metastases and identify recurrent disease (26). The concept for response evaluation is that FDG-PET is performed for initial staging before neoadjuvant therapy and either after a defined number of therapy cycles or at the end of neoadjuvant treatment. All studies report on a decrease in FDG uptake comparing baseline with follow-up FDG-PET in an attempt to define a threshold, using a percentage of decrease in the standard uptake value (SUV) to separate responders from nonresponders. Systematic reviews were performed analysing the value of FDG-PET for response evaluation in the neoadjuvant therapy of patients with esophageal cancer (24,27-29). The first review was published by Westerterp *et al*. in 2005 comparing the diagnostic accuracy of CT, EUS, and FDG-PET for assessment of response to neoadjuvant therapy in patients with esophageal cancer (27). Rebollo Aguirre *et al*. included only prospective studies in their systematic review. With 8 selected articles a ranged sensitivity, specificity, positive predictive value, and negative predictive value for primary tumor response assessment by FDG-PET of 27.3% to 93.3%, 41.7% to 95.2%, 70.8% to 93.3% and 71.4% to 93.5% was calculated suggesting metabolic imaging to be the best available technique for neoadjuvant therapy response assessment in esophageal cancer (29). But all these reviews had the same problem: they included studies using different definitions of response, different cut-off values for the SUV and the time of measurement. The technique of metabolic uptake measurements in FDG-avid tumor may be another critical point. A number of factors influence the results of the SUV measurements which are subject to many sources of variability like patient size, measurement duration, plasma glucose concentration, recovery coefficients, partial volume and region of interest (ROI) selection. In fact, there was no general consensus how to perform SUV measurements and ROI size and position influence results as well as measurement of either average or maximum SUV within the ROI. Therefore, standardized methods of evaluation had to be set up (30).

Further clinical studies could not confirm the clinical relevance of response evaluation with FDG-PET after neoadjuvant therapy (31,32). The results of the prospective study from Piessen *et al*. showed that recurrence was not significantly correlated with the SUV values on restaging. In addition, no significant association was found between metabolic imaging and survival (P=0.106) (32). Other studies confirmed these results (33). In our attempt to address the issue of response evaluation we found considerable overlap between groups at baseline and at the end-of-neoadjuvant therapy PET, which did not allow us to separate histopathologic responders from nonresponders, regardless

of histopathologic type of tumor (adenocarcinomas or squamous cell carcinomas) (34). A principle problem is that these PET scanners do not have microscopic spatial resolution which is required when the aim is to identify only small clusters of viable tumor cells defining the histopathological golden standard. Most of these studies used older imaging techniques of FDG-PET and therefore the data of the newer generation PET scanners and the combination of FDG-PET and computed tomography (CT) are of interest. New evaluation parameters were defined and seem to better correlate with histopathologic response criteria (30). But further evaluation studies are necessary.

Computed tomography (CT)

The risk of tumor progression during neoadjuvant chemoradiotherapy or chemotherapy in esophageal cancer is around 8% to 17% (2). Detection of progressive disease that alters the initial treatment strategy is of great importance, as the majority of these patients is beyond curative treatment and should be refrained from surgery. Therefore a restaging before surgical therapy is necessary. In a recently published study, the authors used small-slice (2/1.5 mm) post-CRT CT scans for adequate radiological assessment of suspect lymph nodes and/or metastatic lesions by two radiologists. Detection of progressive disease before surgery on post-CRT CT prevented futile surgery in 5 (5%) of these patients, but missed progressive disease in 4 (4%) patients (35). The study by Bruzzi *et al*. had distant metastases as primary outcome, comparing CT with PET-CT in the detection of distant metastasis after neoadjuvant chemoradiation. With PET-CT, it was possible to detect distant metastasis in 7 patients (8%) after neoadjuvant CRT, while CT alone detected distant metastasis in 5 (6%) of these patients. Both missed metastases were located outside the range of the routinely performed CT imaging of the chest and abdomen (36). The accuracy of multidetector-row CT (MDCT) for restaging after neoadjuvant treatment in patients with esophageal cancer was studied by Konieczny *et al*. (37). The authors conclude that the diagnostic accuracy of high resolution MDCT for restaging esophageal cancer and assessing the response to neoadjuvant therapy has not improved in comparison to older-generation CT.

Response prediction

Since the introduction of neoadjuvant treatment strategies, either by preoperative chemotherapy alone or in combination with external radiation for the treatment of esophageal cancer, there has been a need for response prediction before the beginning of the treatment or early response assessment identifying responders. Patients who achieve a major histopathological response have a significantly better prognosis than patients with only a minor histopathological response (2,7). Therefore, diagnostic methods for the prediction of response of induction chemotherapy are of interest for individualization of treatment concepts. Until now there are two main ideas for response prediction: measuring the response of the primary tumor by FDG-PET after an initial course of therapy or using molecular markers of the individual patient.

FDG-PET for early prediction of response

There exist several studies that scheduled the subsequent FDG-PET 7-14 days after the initiation of preoperative therapy. For example, Wieder *et al*. demonstrated that FDG-PET is useful for early response prediction in the course of multimodality treatment (38). In 38 patients with esophageal squamous cell cancer they analysed the therapy-induced intratumoral changes of glucose metabolism during radiochemotherapy by performing FDG-PET before and after 2 weeks of initiation of therapy. A significant decrease of intratumoral SUV was detected 2 weeks after initiation of treatment. Moreover, the decrease in SUV was significantly associated with response and prognosis. Similar results from the same institution were found for adenocarcinoma. Based on these findings the working group initiated the single-center MUNICON phase II trial to prospectively evaluate the feasibility of a FDG-PET-response-guided treatment algorithm and its potential effect on prognosis (39). The suitability of FDG-PET for response assessment has been chiefly put forward by one scientific group (38,40,41). Further studies could not confirm these favorable results. Van Heijl *et al*. described a clinical trial comprised serial FDG-PET before and 14 days after start of chemoradiotherapy in patients with potentially curable esophageal carcinoma. Histopathologic responders were defined as patients with no or less than 10% viable tumor cells (major response on resection specimen). FDG-PET response was measured using the SUV. From 100 included patients, 64 were histopathologic responders. The median SUV decrease 14 days after the start of therapy was 30.9% for histopathologic responders and 1.7% for non-responders (P=0.001). Using a 0% SUV decrease cutoff value, PET correctly identified 58 of 64 responders (sensitivity 91%) and 18 of 36 nonresponders

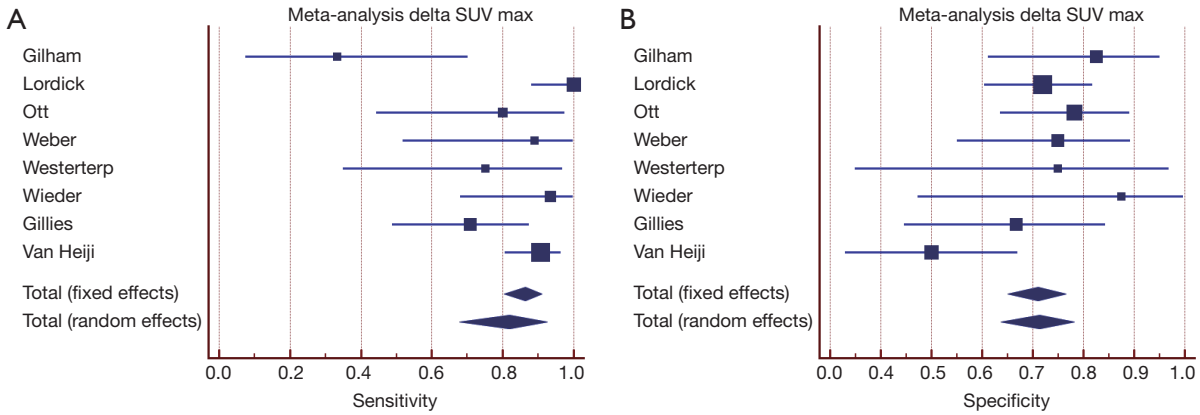

Figure 1 Results of eight studies using FDG-PET for early prediction of tumor response to preoperative chemotherapy or chemoradiation for patients with advanced esophageal cancer. (A) Sensitivity; (B) specificity with the 95% confidence interval for each individual study and the summarized total effects. (The size of the quadrat is equivalent to the number of patients in each study.) SUV, standard uptake value; FDG-PET, fluorodeoxyglucose-positron emission tomography.

(specificity 50%). The corresponding positive and negative predictive values were 76% and 75%, respectively. The authors conclude that the SUV values decrease 14 days after the start of chemoradiotherapy was significantly associated with histopathologic tumor response, but its accuracy in detecting non-responders was too low to justify the clinical use of FDG-PET for early discontinuation of neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer (42).

Figure 1 summarizes of the published literature (41,43-46). The pooled sensitivity was 81% (95% CI: 68-92%) with a significant heterogeneity and the pooled specificity was 71% (95% CI: 64-78%). Summarizing the results of early prediction of responder after neoadjuvant chemoradiation using FDG-PET may be helpful for tailored therapy in esophageal cancer. But there are additional parameters necessary to improve the specificity of this method.

In actual research additional parameters such as entropy, size, and magnitude of local and global heterogeneous and homogeneous tumor regions were used for prediction of tumor response after neoadjuvant chemoradiation and showed promising results for response prediction (47,48). De Cobelli *et al*. used diffusion weighted MRI in 32 patients with gastroesophgeal cancer. The authors found a good correlation between the apparent diffusion coefficient and tumor regression (48).

Molecular markers for response prediction

A large variety of molecular markers has been reported for response prediction of neoadjuvant radiochemotherapy in pre-treatment biopsies reviewed by Fareed *et al*. 2009, Bain *et al*. 2010, Sakai *et al*. 2013, Kaz *et al*. 2014, and Okumura *et al*. 2014 (49-53). However, up to now none of these markers has successfully been applied for guidance of the patients to neoadjuvant treatment or direct surgery with the aim to individualize and thus improve therapy of patients with locally advanced esophageal cancer. The results detected in the "discovery cohorts" are mostly preliminary, require further validation in a larger "qualification cohort" as well as clinical translation. There are no predictive biomarkers established for esophageal cancer treatment.

Genomes, exomes and transcriptoms

Innovative techniques like next generation sequencing (NGS) and exome sequencing have been applied in the efforts to detect mutations with importance for esophageal cancer (54). These techniques provide novel biomarkers with a response predictive value, but should not end at the level of discovery.

There are several retrospective studies evaluating single nucleotide polymorphisms (SNPs) for response prediction in esophageal cancer. SNPs can alter the amino acid sequence, influence RNA splicing or translation efficacy resulting in a changed expression or activity of the proteins encoded. Response predictive impact of gene polymorphisms in pathways involved in therapy response like the DNA repair genes: *ERCC1*, *XRCC1*, *ERCC2* (55), the G-protein *GNAS1*, and the multidrug transport: *ABCB1* gene polymorphisms has been of reported (55-58).

Microarray techniques screening the whole genome for response predictive markers have largely been applied, and identified a huge variety of promising markers (59-63).

Combination of mRNA expression of several predictive markers results in better predictive value than single gene analysis (64,65). For example, in a clinical study with pretreatment biopsies of patients with an advanced esophageal cancer a single marker like Dihydropyrimidine dehydrogenase (DPD) was identified as an independent predictor associated with major response ($P<0.002$). Multivariate analysis of the marker combination of ERCC1, c-erbB-2 syn. Her2-neu, and DPD provided response prediction with 75.0% sensitivity, 81.0% specificity and 78.1% accuracy. Analysis of the marker panel results by Artificial Neuronal Network again showed better predictive values (64).

Thymidylate Synthase and DPD mRNA expression can also be quantified non-invasively in peripheral blood (66).

miRNome

Profiling of miRNAs, the small highly conserved post-transcriptional regulators of gene expression bears a tremendous source for detection of response predictive molecular markers reviewed by Sakai *et al.* and Skinner *et al.* (51,67). Response predictive impact of miRNAs -21, -25, 27b, -99a, -126, 133a, -b, -143, -145, and -192, has been identified (51,68). Since miRNAs are very stable their expression can simply be quantified in serum specimen. This non-invasive marker determination is advantageous for clinical use.

Proteomics

Proteome analysis has been applied for detection of predictive biomarkers by several groups (69-71). Survivin (BIRC5) protein expression has been associated with histomorphological response to neoadjuvant therapy (72). Immunhistochemical detection of ERCC1 and c-erB-B2 syn. Her2-Neu protein expression are two examples for protein markers with response predictive value (72,73).

Further perspectives: translation of research results from bench to bed will be the most crucial future challenge. We have presented a great variety of promising candidates of molecular markers for prediction of tumor response to preoperative chemoradiation. But none of these markers have been introduced in clinical practice. There are some ongoing or just finished trials; e.g., the Pancho trial—which evaluates for the first time whether the p53 genotype is qualified to select patients who will respond to certain chemotherapy and to guide cancer therapy. The results showed that the biomarker TP53 divides esophageal cancer patients into two categories with markedly different outcomes: patients with a normal TP53 marker status may experience notable benefits from neoadjuvant chemotherapy with cisplatin/fluorouracil, whereas those with a mutant TP53 marker status appear to be at risk for lack of response (74). Further results are expected from the Cologne Esophageal Response Predictive (CERP)-study, a prospective clinical study which evaluate the predictive value of ERCC1-SNP in combination with mRNA ERCC1, c-erbB-2 syn. Her2-neu, and DPD in esophageal cancer patients with chemoradiation before surgery.

Another perspective is the combination of imaging procedures and selected molecular markers. Bain *et al.* have reported that higher leptin protein expression were associated with lack of radiological response (75). Studies have shown that prediction with PET in clinical routine had very good sensitivity but was not valid enough to predict "nonresponse" (42). Technical innovations for better imaging of the tumor, expanded response criteria and standardized evaluation may improve the results. But a combination of optimized imaging technic and a well configured marker panel will be the future of response prediction.

The current status of diagnosis, staging, and response prediction with its clinical implications for patients with esophageal cancer is presented in *Figure 2*. Four weeks after preoperative chemoradiation or chemotherapy restaging for response assessment is necessary.

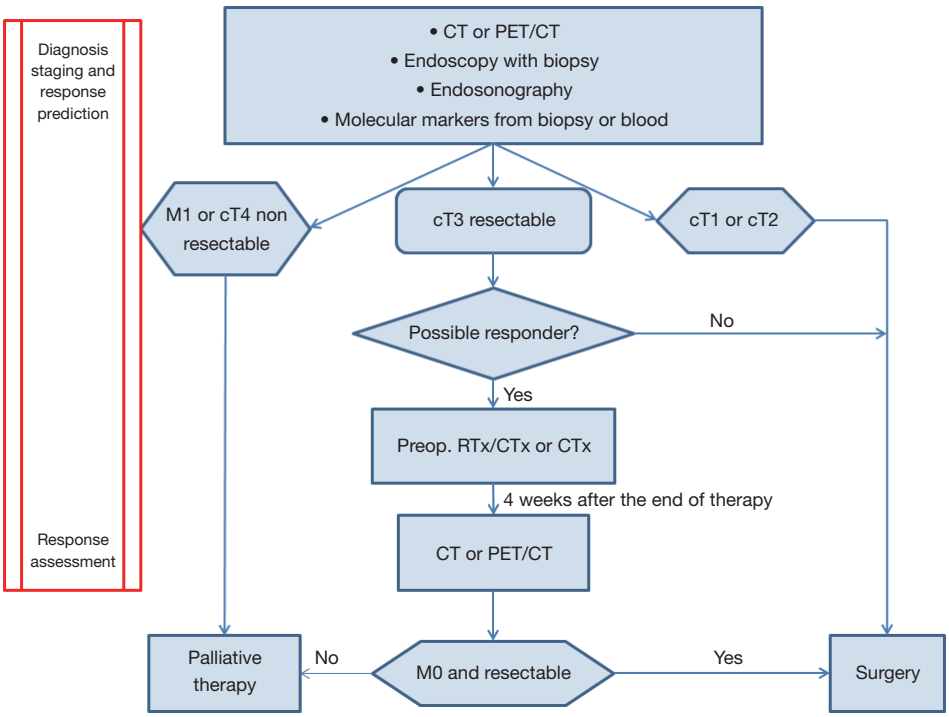

Figure 2 Flowchart for diagnosis, staging, prediction of response and response assessment for curative therapy of patients with advanced esophageal cancer.

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