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Are we there yet?

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Organ sparing management in rectal cancer. Are we there yet?

BACKGROUND: *The "watch and wait" approach has recently been proposed as an alternative to surgery in locally-advanced rectal cancer patients that respond to neo-adjuvant chemoradiotherapy, in order to decrease its negative functional consequences upon the quality of life of these patients. Current methods show low accuracy for the identification of complete responders.*
MATERIALS AND METHODS: *A review of the literature was conducted for articles published up to March 31th, 2019. Relevant studies were identified using bibliographic searches of Pubmed database. The keywords that were used in various combinations were: "neoadjuvant chemoradiotherapy", "non-operative management", "complete pathological response", "rectal cancer", "biomarkers", "staging".*
RESULTS: *Magnetic resonance imaging can identify complete responders with a high accuracy using new protocols like diffusion weighted imaging. Positron emission tomography with 18-fluoro-deoxy-glucose shows a sensitivity of 90.9% and specificity of 80.3% for the prediction of complete pathologic response using the change in standardized uptake value. A panel of 15 metabolites was identified and shows potential to discriminate patient resistance and sensitivity to neo-adjuvant therapy (Area Under the Curve 0.80). Furthermore, pre-treatment peripheral blood neutrophil to lymphocyte ratio below 2 and platelet to lymphocyte ratio below 133.4 are significantly correlated with good tumor response (OR 2.49). Analysis of the pattern of carcinoembryonic antigen (CEA) clearance after neoadjuvant treatment conclude that an exponential decrease of the CEA levels is associated with significant tumor down staging and complete pathologic response.*
CONCLUSION: *New methods of assessing the response to neo-adjuvant therapy in locally-advanced rectal cancer have emerged, showing promising results. Further studies need to assess the best combination between imaging and these biomarkers in order to increase the accuracy and standardize the criteria for non-operative management.*

KEY WORDS: Biomarkers, Complete pathologic response, Non-Operative management, Rectal cancer, Staging.

Introduction

Rectal cancer represents approximately 30% of colorectal adenocarcinomas and is usually associated with an adverse prognosis [1]. Locally-advanced rectal cancer is defined as T3-4 N0 or any T with positive lymph-nodes

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disease. The standard of care for these patients is represented by neo-adjuvant chemotherapy and radiotherapy, followed at 6-8 weeks by surgical resection, as this protocol has demonstrated the best oncological outcomes when compared to radiotherapy or surgery alone [2,3].
Depending on the location of the disease, surgical resection might involve low anterior rectal resection (LAR) with total mesorectal excision (TME) or abdominoperineal resection (APR). A major surgery like this entails a high morbidity for the patients, with reported perioperative mortality rates ranging from 4% in the general population to 30% in the elderly [4]. Anastomotic leaks can be found in up to 7% of the patients [5]. Furthermore, one third of the patients that undergo pre-operative chemo-radiation followed by surgery experience functional complications like urinary toxicity, sexual dysfunction, bowel urgency, fecal incontinence [6,7]. Having a permanent ostomy alters significantly the quality of life of these patients, with 32% of the subjects reporting a moderate-to-severe impact [8], with worse physical and role functioning as well as worse body image in comparison with patients that undergo sphincter preservation surgery [9].
The purpose of neo-adjuvant chemo-radiotherapy is to obtain the down-staging of the disease in order to allow the possibility of a curative surgical approach and improved functional outcomes: avoidance of a permanent colostomy and sphincter preservation [10]. Moreover, neo-adjuvant chemo-radiotherapy might even achieve complete pathologic response (ypT0) in up to 20% of the cases [11,12], which opens the pathway towards an organ-preservation strategy, as operating patients with complete pathologic response could be considered overtreatment. Multiple studies have shown that complete pathologic response is correlated with better oncologic outcomes, like a lower recurrence rate, improved disease-free survival and overall survival [13,14] regardless of the initial clinical T and N stage [15]. Furthermore, a systematic review by Fiorica et al [16] concluded that major surgery in these patients does not improve the prognosis or the 5-year oncologic outcomes.
In this context, a "watch and wait" approach [17] has emerged in order to avoid the morbidity and the negative functional outcomes of the surgery, but its results are strictly dependent on the possibility of accurately identifying the patients with complete response to neo-adjuvant chemo-radiotherapy, as tumor persistence is an imperative indication for further treatment. Clinical complete response is defined as the lack of clinical, endoscopic or radiographic evidence of disease, whereas pathologic complete response can only be assessed after surgery and involves no detectable tumor cells [18]. In up to 7% of patients, the clinical and pathologic complete response are not concordant, thus new methods need to identified in order to avoid under/overtreatment [19].

Current methods to assess complete pathologic response

The current non-surgical modalities to assess the response to neo-adjuvant chemo-radiotherapy are physical examination, endorectal ultrasound, endoscopy, computed-tomography (CT) and magnetic resonance imaging (MRI) [20]. The success of the watch and wait approach is warranted by the degree of similarity between the clinical and pathological complete response, which is still a problem.
Digital rectal examination underestimates the pathologic response to neo-adjuvant chemo-radiotherapy in 78% of cases and should not be used alone to assess the efficacy of the treatment [21]. Mucosal integrity examination, endorectal ultrasound and MRI have also poor accuracy for the prediction of complete pathologic response, either alone or in combination, with a sensitivity as low as 25%, as shown by Liu et al [22]. Because of peritumoral inflammation, the desmoplasic reaction is an important drawback of endorectal ultrasound, which usually overstages early rectal cancer to a T2-T3 lesion. The tendency to overstage occurs more often after neoadjuvant treatment because of the alteration of rectal and perirectal tissues, endorectal ultrasound being unable to identify residual carcinoma in postradic degeneration and fibrotic tissue [23].
Furthermore, as shown by Hiotis et al [24] on a group of 488 patients, the concordance between clinical and pathological complete response is around 25 % if clinical examination and proctoscopy are performed for the assessment of response. As a result, the same authors conclude that a watch and wait approach based on the available clinical information is not safe and should not be performed.
Confirming the findings of Liu et al, Renehean et al [25] reported that a third of the patients with clinical complete response assessed by the current methods show local recurrence, probably due to the persistence of tumor cells in the submucosa or muscle layer of the rectal wall [26], and some of these cases are not even suitable for salvage resection [27]. On the other hand, no significant impact on survival was identified when comparing clinical complete response patients and pathologic complete response if intensive follow-up and salvage surgery were performed [28]. Still, the criteria for the assessment of complete clinical response is often imprecise and varies between centers. The presence of any tumor, superficial or deep ulceration, any palpable nodule or stenosis should prompt immediate surgical treatment as they suggest the persistence of the disease. Habr-Gama et al [29] identified a number of features that can be present in complete clinical response patients and should not be considered as residual disease: whitening of the mucosa, teleangiectasia with mucosal integrity and loss of pliability of the rectal wall during insufflation.

The standardization of complete clinical response is one of the main steps towards a safe implementation of the watch and wait approach. Furthermore, there is a critical need to identify new methods or biomarkers that could improve the prediction accuracy for the complete pathologic response to neo-adjuvant chemo-radiotherapy in locally-advanced rectal cancer patients.

Prediction factors for complete pathologic response

A number of prediction factors have been evaluated and have shown a potential to predict the response to neo-adjuvant treatment.

Clinical

Until present, the most studied and consistent predictors of complete response are the tumor dimension, TNM stage and grade.
In a retrospective review performed by Al-Sukhni et al [30] which included 23.747 patients, the authors conclude that the patients who are most likely to respond to neo-adjuvant chemo-radiation harbor low-grade tumors and low clinical T and N stages. A complete pathologic response is well predicted by a pre-treatment tumor size below 5 cm [31]. Also, clinical T1-3 stage has a 1.808 HR for the prediction of complete pathologic response in comparison with cT4, p=0.031, as shown by Peng et al on a group of 297 patients [32]. An undifferentiated rectal tumor has lower Odds Ratio for complete pathologic response in comparison with a moderately differentiated tumor (OR 0.78 vs 1.01, p=0.002) [30]. Furthermore, pre-chemoradiotherapy tumor mobility is also a significant predictor of complete pathologic response as shown by Park et al [33].

MRI

Dynamic contrast-enhanced MRI is usually employed for rectal cancer assessment, but the accuracy in the prediction of complete response is low, due to the fibrosis that appears after neo-adjuvant chemo-radiotherapy and impairs the discrimination from residual tumor, with poor interobserver agreement [34]. Still, Rengo et al [35] propose an MRI automatic fibrosis quantification model on T2 weighted images, which has shown a good correlation with the pathological examination (kappa 0.91), in comparison with manual quantification of the fibrosis in a group of 65 patients. The authors identified a cut-off of 81% fibrosis that could predict the complete pathologic response with a Se of 78.26% and a Sp of 97.62%. Furthermore, a new MRI technique, diffusion weighted imaging (DWI), quantified by the apparent diffusion coefficient (ADC), has gained more and more interest in the last years. Diffusion weighted imaging assesses the water movement into the tissues. A high cell density, which is characteristic for neoplasia, will lead to the restriction of the water molecules movement. In a systematic review by Amodeo et al [36], the authors concluded that DWI is a promising technique to assess the complete pathologic response to neo-adjuvant chemo-radiotherapy with the difference between pre-treatment and post-treatment ADC showing the highest accuracy in discriminating complete responders (Sensitivity 83.2%, Specificity 80.6%, AUC 0.895).

Positron emission tomography with [18] fluoro-deoxy-glucose ([18]-FDG-PET)

[18F] FDG-PET is a functional imaging modality that has shown promising results for evaluating various oncological diseases [37]. In rectal cancer, the results of the studies published until recently are heterogenous. Baseline PET-CT performed before the beginning of chemoradiation has shown an accuracy of 44% for the prediction of complete pathologic response, thus it is not included into the standard evaluation protocol of locally-advanced rectal cancer patients [38].
The metabolic changes that occur during neo-adjuvant treatment for rectal cancer precede the morphological ones and can be identified by FDG-PET even from the second week after the beginning of treatment, thus this information can be useful for the prediction of tumor response to chemoradiotherapy. Maffione et al [39] performed a systematic review including 10 studies and 302 patients with locally-advanced rectal cancer, who underwent neo-adjuvant treatment and certified a high accuracy of FDG-PET if the response index (percentage decrease of SUV) was used for the assessment: Se 82%, Sp 85%, cut-off 42%. Koo et al confirmed the previous conclusions and identified a Se of 90.9% and Sp of 80.3% for the prediction of complete pathologic response using the change in SUV, as well [40]. Another parameter that could be used for the prediction of response after completion of neoadjuvant treatment is tumor SUVmax normalized to liver uptake (SLR), as proposed by Park et al [41]. The authors showed that SLR has the highest accuracy for the prediction of tumor response (AUC 0.826) in comparison with other FDG-PET derived parameters.
In conclusion, FDG-PET has the possibility of adding valuable information for rectal cancer patients management, but further attention should be focused on the dynamic changes in SUV during the course of treatment and after the neoadjuvant chemoradiotherapy, as well as on new FDG-PET derived parameters.

Metabolomics

The metabolomic profile encompasses all the changes that occur in a system as response to the presence of a dis-

ease by the identification of different small metabolites resulted from intracellular reactions. Thus, in altered metabolic pathways such as in cancer, the metabolomics profile could offer new disease-specific biomarkers, which may improve the diagnosis and prognosis of these patients. The metabolomics analysis is usually performed by gas chromatography/ mass spectrometry and nuclear magnetic resonance.

Chan et al [42] analyzed a group of 31 patients with colorectal carcinoma and identified more than 20 significantly altered metabolite levels in tissue samples from the tumor and normal mucosa, of whom choline-containing compounds, taurine, scyllo-inositol, lactate and phosphocholine were present in significantly higher concentrations in colorectal cancer tissue samples. Qiu et al [43] also confirmed the possibility that metabolomics could discriminate between patients with or without colorectal cancer using serum samples analysis.

Jia et al [44] analyzed the role of metabolomics for the prediction of the pathologic response to neo-adjuvant treatment on a group of 105 patients with locally-advanced rectal carcinoma. The serum samples were obtained before the start of chemoradiation. A panel of 15 metabolites was identified and showed an AUC 0.8 for the discrimination between neo-adjuvant therapy sensitive and resistant patients. Furthermore, after mapping the metabolites, the authors concluded that the dysregulation of the histidine, glycine, serine, threonine and glycerophospholipid metabolism is correlated with the response to neo-adjuvant chemoradiation and might be of great importance for future treatment strategy.

Inflammation

Although tumor intrinsic characteristics were thought to be the sole determinants of the response to treatment, recent studies identified also host factors that could contribute to the resistance or sensitivity to therapy. The degree of systemic inflammation seems to be predictive of the recurrence rate and survival of cancer patients, as it leads to a tumorigenic microenvironment, promoting cell proliferation, local invasion and metastasis [45]. Among the inflammatory markers that were reported to be linked with the oncological prognosis there have been described: the number of lymphocytes, platelets, neutrophils, monocytes or derived ratios (lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio etc), C-reactive protein, serum albumin, interleukin and Glasgow Prognostic Scale [46].

In rectal cancer, baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be used to predict tumor regression after neo-adjuvant chemoradiotherapy. Kim et al [47] has shown that a pre-treatment NLR below 2 and PLR below 133.4 are significantly correlated with good tumor response (OR 2.49) in a group of 176 patients with locally-advanced rectal cancer. Lee et al analyzed also the white blood cell (WBC) dynamics during neo-adjuvant treatment, and observed that a low WBC ratio (the lowest count of WBC during radiochemotherapy/initial WBC count) is associated with higher rates of complete pathologic response: 23.8% in low WBC ratio vs 12.2% in high WBC ratio, p=0.001 [48].

Others

The carcinoembryonic antigen (CEA) is serum biomarker used during the follow-up colorectal cancer patients, as it has shown significant correlation with the oncological outcomes [49]. Low pre-treatment CEA, as well as CEA normalization after neo-adjuvant treatment, seem to be associated with complete pathologic response to chemoradiotherapy [50,51], but the results of the studies are still heterogenous. Hu et al [52] propose a new analysis of the pattern of CEA clearance after neoadjuvant treatment and conclude that an exponential decrease of the CEA levels is associated with significant tumor downstaging and complete pathologic response (OR 5.22, p=0.04).

Other biomarkers have been assessed with regards to the prediction of rectal cancer response to neoadjuvant chemoradiation, but validation is still awaited. Huh et al [53] reported that pre-treatment high levels of CD44 mRNA might correlate with a poor response, whereas Yan et al supports a potentially useful role of SMac, Ki-67, VEGF for the prediction of rectal tumor behaviour [54].

Cost efficiency

As the number of patients undergoing the wait and see approach increases, questions have been raised regarding the costs associated with the sequential scans needed for the close follow-up of these patients. Gani et al [55] performed a cost analysis of rectal cancer patients that undergo neoadjuvant treatment and surveillance using MRI and rectoscopy and compared these data with the costs of immediate surgery. The authors concluded that a watch and wait approach with an intensive surveillance protocol has lower costs in comparison with immediate surgery, even when considering 25% of patients experiencing local regrowth and requiring salvage surgery.

Conclusion

As more efficient oncologic treatment has been developed, the long term quality of life of cancer patients has become of tremendous importance. The possibility to identify the patients with complete response to neo-adjuvant chemoradiotherapy opens the pathway towards a

conservative approach. Current assessment strategy lacks the accuracy for the identification of such patients. New methods of assessment have emerged and have the potential to become adjuncts in the evaluation of complete response. A small, mobile and well differentiated rectal tumor is more likely to completely respond to neo-adjuvant treatment. MRI and FDG-PET can identify complete responders with a high accuracy using new protocols like DWI, fibrosis quantification or dynamic sequential scans, but standardization of the protocols is needed. Clinical prediction factors, combined with metabolomics, inflammatory or other biomarkers have the potential to become the new standard due to their wide availability and non-invasiveness. Future studies need to assess the best combination between imaging and these biomarkers in order to increase the accuracy for the identification of complete responders to neoadjuvant chemoradiotherapy.

Riassunto

L'approccio "watch and wait" è stato recentemente proposto come alternativa alla chirurgia in pazienti con carcinoma del retto localmente avanzato che rispondono alla chemio-radioterapia neo-adiuvante, al fine di ridurre le sue conseguenze funzionali negative sulla qualità della vita di questi pazienti. I metodi attuali mostrano una bassa accuratezza per l'identificazione di responder completi.

È stata condotta una revisione della letteratura per articoli pubblicati fino al 31 marzo 2019. Gli studi rilevanti sono stati identificati utilizzando le ricerche bibliografiche del database Pubmed. Le parole chiave utilizzate in varie combinazioni erano: "neoadjuvant chemoradiotherapy", "non-operative management", "complete pathological response", "rectal cancer", "biomarkers", "staging".

Risultati: la risonanza magnetica può identificare i responders completi con un'accuratezza elevata utilizzando nuovi protocolli come l'imaging pesato in diffusione. La tomografia ad emissione di positroni con 18-fluorodeossi-glucosio mostra una sensibilità del 90,9% e una specificità dell'80,3% per la previsione della risposta patologica completa utilizzando il cambiamento nel valore di captazione standardizzato. Un gruppo di 15 metaboliti è stato identificato e mostra la possibilità di discriminare la resistenza e la sensibilità del paziente alla terapia neoadiuvante (Area Under the Curve 0,80). Inoltre, la neutrofilia periferica pre-trattamento il rapporto linfocitario inferiore a 2 e il rapporto piastrinico-linfocitario inferiore a 133,4 sono significativamente correlati con una buona risposta tumorale (OR 2,49). L'analisi del pattern di clearance dell'antigene carcinoembrionico (CEA) dopo il trattamento con neoadiuvante porta a concludere che una diminuzione esponenziale dei livelli di CEA è associata a un significativo decadimento del tumore e alla completa risposta patologica.

In conclusione sono emersi nuovi metodi per valutare la risposta alla terapia neo-adiuvante nel carcinoma del retto localmente avanzato, mostrando risultati promettenti. Ulteriori studi devono valutare la migliore combinazione tra imaging e questi biomarcatori al fine di aumentare l'accuratezza e standardizzare i criteri per la gestione non operativa.

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