Watch and Wait Strategy for Rectal Cancer: 15 Years After the First Published Study. Are We any Closer to the Non-operative Management of Rectal Cancer?

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Strategia Watch and Wait pentru cancerul de rect: 15 ani de la primul studiu publicat. Sunt mai aproape de tratamentul non-operator al cancerului de rect?

Introducere: De-a lungul timpului, tratamentul cancerului rectal a evoluat semnificativ prin utilizarea sporită a radiochimioterapiei neoadjuvante.

Material și metoda: Ghidul P.I.C.O.S a fost utilizat pentru a structura întrebările și topica cercetării în vederea obținerii validității clinice. Rezultatele obținute au fost filtrate conform ghidului PRISMA.

Rezultate: Am identificat un număr de 42 de lucrări, după screening-ul acestora, au rămas 27 pentru a completa cercetarea.

Discuții: Există un interes crescut față de managementul neo-operator al cancerului rectal întrucât până la 25% dintre pacienții supuși unui regim de radiochimioterapie preoperatorie au demonstrat răspuns patologic complet (absența celulelor tumorale pe specimenele rezecate). Aceste informații conduc la ideea atrăgătoare că, în unele cazuri, intervenția chirurgicală poate fi evitată. Din nefericire, există o lipsă de date de calitate pentru a susține această nouă tendință. Datorită interesului recent crescut, are creată o bază de date internațională în care pacienții aflați în perioada de w&w pot fi înscriși și monitorizați. Până în prezent, baza de date conține peste 900 de pacienți. De asemenea, sunt în curs de finalizare studii prospective de calitate.

Concluzii: Cu toate aceste eforturi recente, utilizarea pe scară largă
Watch and wait strategy in rectal cancer

Introduction
Colorectal cancer occupies at the moment the number three place in the world ranking of the most prevailing neoplasms (1). The treatment of colorectal cancer through adjuvant and neo-adjuvant therapies has evolved significantly over time (2). However, surgery remains the pillar of the treatment strategy (3). The standard treatment in stage II and III is surgical resection with total mesorectal excision (TME) and neo-adjuvant radiotherapy/chemotherapy (4). Of all the patients who undergo neo-adjuvant therapy and surgery, up to 25% have a complete pathological response on the resected specimen (no tumor cells are identified at the histopathological examination) (4). The standard surgical interventions for rectal cancer are low anterior resection or abdomino-perineal resection, both with TME. These interventions have important perioperative morbidity. Up to 11% of these patients develop a fistula and up to 15% have a permanent stomy with an important decrease in the quality of life (5-7). Development of minimally invasive techniques such as laparoscopy does not seem to influence the rate of these complications (8).

Taking into account all these risks, solutions such as neo-adjuvant therapy have been sought which may offer a complete clinical and pathological response (9). With the introduction of this new treatment strategy, other problems occur which refer to the definition of complete clinical response. In the case of resection, complete pathological response is defined as the absence of tumor cells on the examined specimen, but complete clinical response is inaccurately defined as it includes multiple criteria: the absence of rectal ulceration, absence of rectal stenosis, absence of a rectal mass at rectoscopy (10,11). These two forms of assessment (pathological response and clinical response) are not

Abstract
Introduction: Over time, the management of rectal cancer has undoubtedly evolved with the use of neo-adjuvant radiochemotherapy.
Material and method: The P.I.C.O.S guidelines were used to structure the questions and the research topic as to attain clinical validity. The results of the research were filtered in accordance with the PRISMA checklist.
Results: We identified 42 papers. After screening 27 papers were used to complete the analysis.
Discussion: There is an increased interest towards the non-operative management of rectal cancer, as up to 25% of patients with preoperative radiochemotherapy have demonstrated complete pathological response (absence of tumor cells on the operative specimens). This information leads to the tantalizing idea that in some cases, surgery can be avoided. Unfortunately, there is a lack of quality data to support this view. Due to increased interest in this subject, an international database in which patients with w&w therapy can be enrolled and monitored. Up to now, the database contains over 900 patients. Also, quality prospective trials are emerging.
Conclusion: Even with all these recent efforts, the wide-use of this therapy is precluded due to the absence of a standardized evaluation of these patients in the follow-up period.

Key words: non-operative treatment, rectal cancer, watch and wait

Cuvinte cheie: tratament non-operator, cancer de rect, watch and wait

a acestei terapii este împiedicată de absența unei evaluări standardizate a acestor pacienți în timpul perioadei de urmărire.
always consistent with each other (12). Complete clinical response was reported in up to 40% of the cases with neoadjuvant treatment (13,14). After surgery, it was observed that half of these resected specimens contained tumor cells at histopathology examination (13,14). Therefore the criteria of selection and safety of w&w strategy raise serious question marks (13,14).

In 2004, an article was published by a group of Brazilian researchers who questioned decades of treatment and research in colorectal cancer, investigating comparatively two groups of patients (with and without surgery) who had complete clinical response after neoadjuvant treatment (15). Following the analysis of the results, they concluded that there were no differences in survival between the two groups of patients (15). A new treatment strategy had been defined - watch and wait (w&w) or active surveillance as an alternative to surgery (16).

In the w&w strategy, patients may refuse scheduled surgery after neoadjuvant radiotherapy. After long radiotherapy course (45-65 Gy), they will enter a surveillance program that includes regular MRI, rectoscopy and rectal examination. Although promising, these results have not been reproduced uniformly in randomized trials, so the safety of this procedure remains questionable.

The purpose of this review was to analyze the data published in the literature on this extremely attractive topic which gains momentum.

**Material and Method**

The research was performed using the PubMed database. The P.I.C.O.S concept (patient, intervention, comparator, outcome, study type) was used to structure the questions and the research topic as to attain clinical validity. The results of the search were filtered in accordance with the PRISMA checklist (Preferred Reporting Items for Reviews and Meta-Analysis). We used the standard recommendation of two independent readers who performed the selection and subsequent extraction process.

**Results**

We identified 42 papers from one medical database. After exclusion of 8 papers (duplicates), the number was reduced to 34. Of these, 4 papers were not obtainable while other 3 papers were not appropriate for the research subject. 27 papers were used to complete the analysis.

**Discussion**

Historically, colorectal cancer has been associated with a rather poor prognosis, but with the standardization of its treatment, including neoadjuvant chemoradiotherapy and TME in surgery, there was a drastic reduction in the number of recurrences including in advanced tumors (17). The primary goal of neoadjuvant radiotherapy was to reduce tumor volume and increase the number of surgical procedures that save the anal sphincter. There are currently no clear criteria to guide a patient towards a w&w strategy (18). Most studies published in the literature are of poor quality, retrospective with heterogeneous populations in terms of age, tumor staging and comorbidities. This lack of homogeneity in the analyzed populations results largely from the fact that the decision maker is ultimately the patient. Also, the experience of hospitals with this treatment strategy is limited. All of this translates into increased variability of the reported regrowth rates that is difficult to ignore. This variability ranges between 3.3% and 33% (19).

The current trend of evidence-based medicine is defined as an approach to medical practice intended to optimize decision-making by emphasizing the use of evidence from well-designed and well-conducted research obliges the clinician to pay increased attention to the design of the study so he can safely apply the results in his practice. Keeping this in mind, as of November 2018, there were no published prospective randomized trials on this subject (20).

There is however, one ongoing prospective trial, the results are due to be published this
year. It compares subjects which have locally advanced rectal tumors who had complete clinical response after neoadjuvant chemoradiotherapy based on the w&w strategy and patients with surgical intervention. The end-point was the oncological outcome after a three-year interval (21). Data on this topic indicates that there is no difference in survival until regrowth between w&w patients with a complete clinical response and patients who undergo surgery after a 2-year follow-up interval (22,23).

Up to 25% of patients who undergo neoadjuvant combined radiochemotherapy have a complete pathological response (absence of tumor cells on the histopathology reports) (24,25). Most of the recurrences occur in the first two years after completion of radiochemotherapy. Up to 30% of these patients will require a surgical intervention due to regrowth, and over 80% of them are surgically treated without a notable impact on survival compared to patients who had undergone surgery immediately after neoadjuvant therapy (26). Kong JC evaluated in a review published in 2017 the percentage of sphincter-saving procedures of the patients with regrowth in the w&w protocol. He noted that in 84% of these patients, sphincter salvage surgery could be performed without a difference in overall survival compared to patients undergoing surgery first (27).

The proportion of patients with initially unresectable tumors at diagnosis who underwent surgery after the w&w protocol is not known. There is currently no standard follow-up protocol, each clinic has its own surveillance programme. Steps towards standardization are being made. An International database for patients under the w&w protocol has been set up to track the evolution of a large population from multiple centers all over the globe, in an attempt to deliver clinically applicable results. This database currently contains approximately 900 patients with rectal tumors who had a complete clinical response to neoadjuvant therapy. The problem with this database is that it does not contain the second arm of patients with surgery to whom it can be compared (26).

The selection process for this therapy is difficult and non-standardised. It is important that these patients understand that up to 30% of them will have residual tumor tissue despite the apparent complete clinical response (26).

Currently, treatment guidelines in the United Kingdom, recommend this strategy to patients, as long as they are informed that it is still in the experimental stages (28). In the European Union, the European Oncology Association (ESMO) recommends the w&w strategy for high-risk patients. Again, uncertainty exists regarding the definition of such criteria as “high risk” as they are not clearly defined (29).

**Conclusion**

Non-operative management with complete clinical response after neoadjuvant chemoradiotherapy may represent an option for some selected cases of rectal cancer only after the patient is informed about the limitations of this therapy. Although the concept of w&w therapy has seen an increase in supportive data, its widespread use is precluded due to the absence of high quality, high volume prospective studies which translate in a lack of standardization of the treatment strategy.

**Conflicts of interests**

The authors declare no conflicts of interest.

**Authors Contributions**

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Conflict of Interest
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