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Review Article

Timing of neoadjuvant therapy and surgical treatment in rectal cancer

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ABSTRACT

Study objectives: To evaluate the ideal timing between neoadjuvant therapy and surgical treatment of rectal cancer, as well as the influence on treatment outcomes.
Methods: Using PubMed, a systematic literature search was made on the influence of surgery timing after chemoradiotherapy in treating rectal cancer.
Results and discussion: A total of 34 articles published until April 2017 were analyzed. Nine of them were randomized clinical trials, one was a non-randomized trial, 23 were retrospective studies, and one was a meta-analysis. These studies compared treatment intervals varying between two and 19 weeks. Intervals of nine to 14 weeks showed increased tumor downstaging and higher rates of complete pathological response. These intervals shown safety for patients. Nonetheless, few studies showed differences in overall survival. The most used intervals between neoadjuvant chemoradiotherapy are six to eight weeks. Despite that, intervals longer than these show potential benefits for patients without putting them at risk of disease progression. Studies evaluating the effect of overall survival and long-term recurrence are scarce.
Conclusion: Programming surgery more than eight weeks after chemoradiotherapy seems preferable to the six to eight weeks most recently practiced, increasing tumor downstaging and having higher complete pathological response rates.

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Palavras-chave:
Procedimentos cirúrgicos operatórios

RESUMO

Objetivos do estudo: Avaliar o timing ideal entre a terapêutica neoadjuvante e cirúrgica no carcinoma do reto e a sua influência nos outcomes de tratamento.

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Material e métodos: Utilizando a "PubMed", foi feita uma revisão sistemática da literatura disponível acerca da influência do timing cirúrgico após quimiorradioterapia neoadjuvante no tratamento do carcinoma do reto.
Resultados e discussão: Foram analisados 34 artigos publicados até Abril de 2017, sendo que destes nove foram ensaios clínicos randomizados, um foi ensaio clínico não randomizado, 23 foram estudos retrospetivos e um foi uma meta-análise. Estes estudos compararam intervalos de tratamento que variaram entre 2 e 19 semanas. Intervalos entre as 9–14 semanas demonstraram aumento do downstaging tumoral e da taxa de resposta patológica completa. Estes intervalos demonstraram segurança para os doentes. Contudo, poucos estudos demonstraram diferenças na sobrevida dos doentes. Os intervalos mais usados entre a QRT neoadjuvante e o tratamento cirúrgico são de 6–8 semanas. Apesar disso, intervalos superiores às 6–8 semanas demonstram potenciais benefícios para os pacientes sem os colocar em risco de progressão da doença. São limitados os estudos que avaliam o efeito na sobrevida e recorrência em longo prazo.
Conclusão: A programação da cirurgia superior às 8 semanas após quimiorradioterapia parece ser preferível às 6–8 semanas até recentemente praticada, aumentando o downstaging tumoral e a taxa de resposta patológica completa.

Introduction

Worldwide, it is estimated that a total of 1,573,000 individuals were diagnosed with colorectal carcinoma (CRC) in 2013, and that 771,000 died of this same disease. CRC is the third most common malignant neoplasm, and the fourth leading cause of death by cancer.[1] Rectal carcinoma accounts for approximately one-third of these cases. The term locally advanced rectal carcinoma (LARC) has been used to describe various entities.[2] However, in most cases it refers to rectal tumors that invade the mesorectum and adjacent organs or structures (T3/T4) or reach the lymph nodes (N+). In the last decades, its treatment has been based on the combination of surgery (with complete mesorectal excision), radiotherapy (fractioned or hypofractionated), and chemotherapy (radiosensitivity inducing or systemic). In addition to improvements in the field of imaging, surgery, and pathology, the use of this multimodal approach[3–6] has led to a lower rate of local recurrence and improved patient survival.[7,8]

One of the issues to be clarified in the treatment of LARC is the optimization of the available treatments and their timing. In most centers, patients are treated with neoadjuvant therapy followed by surgery, with or without postoperative adjuvant therapy. Some studies[9] argue that there is little evidence to support this paradigm, which is based mainly on only two clinical trials (CAO/ARO/AIO-94 and MRC-07) that assessed the optimal timing between neoadjuvant therapy and surgery.[10,11]

Other studies have demonstrated that radiotherapy combined with chemotherapy is the most commonly used neoadjuvant modality in LARC.[12–14] Combined with surgery, this modality is associated with lower toxicity and better local control.[14,15] The benefits of neoadjuvant chemoradiotherapy (CHRT) include patient adherence, pathological tumor response that allows for complete surgical resection, decreased risk of locoregional recurrence, and reduction of the clinical stage of the tumor.[12,13,16–18]

Traditionally, it was believed that a potentially growing tumor after neoadjuvant CHRT could be detrimental to patient survival and also increase surgical complexity. Higher intervals may result in increased tumor regression and increased R0 surgical margins. Conversely, short intervals may hinder surgical resection due to edema in the surrounding rectal tissues. An excessively long interval may lead to surgical complications due to pelvic fibrosis, induced by radiotherapy, which would impact surgical resection, perioperative morbidity, and quality of life.[19]

Currently, international guidelines recommend that patients with LARC who are candidates for neoadjuvant therapy should undergo surgery within six to eight weeks (ESMO) or five to 12 weeks (NCCN) after completion of long-term CHRT.[20,21] These recommendations are mainly based on clinical trials that established the definitive role of neoadjuvant radiotherapy in LARC.[10,22] However, there is no consensus regarding the optimal interval between CHRT and surgery.

In this article, the authors reviewed the available literature on the timing of neoadjuvant CHRT and surgical treatment in the squamous cell carcinoma, focusing especially on the interval between these two therapies and their influence on oncological outcomes.

Materials and methods

A literature search was conducted in the PubMed database in November 2017 using the following MeSH terms: "neoadjuvant therapy" and "rectal cancer" and "timing of surgery" and "surgical treatment", limiting the date of publication to studies published until November 2017. A language filter was used to search only for articles in English or Portuguese. A total of 75 articles were retrieved. The exclusion criteria were: review articles, comments, and letters; colon carcinoma; different study objectives, full article availability. Thus, 45 potentially relevant articles were selected by reviewing the title and

abstract. A total of 34 articles were included in this systematic literature review.

Results and discussion

Characteristics and results of the 34 articles

Types of studies: Nine were randomized, non-blinded, controlled trials[7,8,23–29]; one was a non-randomized, non-blinded, controlled clinical trial,[30] 23 were retrospective studies[31–53]; and one was a meta-analysis.[54]

Timing between neoadjuvant therapy and surgical treatment

The studies were very heterogeneous in the definition and comparison of time intervals. Some studies established the median time intervals and created one group at intervals lower than this median and one at higher intervals (six to eight, seven, eight, or 12 weeks, *etc.*).[33,34,39,42,44–48,50,51] Some studies divided patients into groups with different intervals and compared the outcomes (<six weeks, six to eight weeks and >eight weeks, seven to eight weeks, nine to ten weeks, 11–12 weeks, *etc.*).[7,8,24,25,28,35,37,38,40,52,54] Other studies compared intervals from one week to another (four *vs.* six to eight weeks, four *vs.* eight weeks, six *vs.* 12 weeks, seven *vs.* 11 weeks, nine *vs.* 14 weeks, *etc.*).[23,26,27,30,32,43] This was a limitation of the present review, since the variance of the intervals hinders the systematic analysis of the results of the studies. In total, studies with intervals of two to 19 weeks were included.

Objectives

The study assessed the influence of treatment timings on pre-surgical imaging staging and on oncological outcomes in the short term (type of resection, complete pathologic response, tumor response, surgical margins, and perioperative morbidity and mortality) and long term (local recurrence rate, distant metastasis, and disease-free survival). The fact that not all selected studies assessed the same treatment outcomes hindered the comparison of the results, which is another limitation of the present review.

Imaging evaluation

Studies comparing imaging evolution by nuclear magnetic resonance imaging of tumor volume before and after CHRT indicate that, on average, the initial tumor volume is reduced by 50% after 14 days. It is also estimated that 20 weeks would be necessary to a medium-sized tumor (54 cm^3) to reach volumes below 0.1 cm^3.[31]

In LARC, the peak tumor downstaging and tumor volume decrease observed by imaging is at 14 weeks.[32]

The potential benefit of postponing surgery should be weighted against its possible risks. The latter include the risk of tumor growth or development of metastases, perioperative complications, and late onset of adjuvant chemotherapy after surgery in the indicated cases.[7,8]

Outcomes according to surgical timing

Currently, most of the data on the influence of surgical timing on cancer outcomes are limited to retrospective studies.[33–54] Therefore, randomized clinical trials in patients with LARC are being conducted to assess short-term outcomes (type of resection, complete pathological response, tumor response, surgical margins, and perioperative morbidity and mortality) and long-term (local recurrence, distant metastasis, and disease-free survival) after CHRT, according to time to surgery.[23,29]

Short-term outcomes

Type of resection

Initially, the study of the optimization of surgical timing after CHRT aimed to evaluate its impact on the type of resection, namely whether postponing the surgery until six to eight weeks (in T3/4), with the consequent increase in tumor downstaging, would lead to higher rates of conservative sphincter procedures. However, no statistically significant results were obtained.[24] That randomized clinical trial assessed secondary endpoints such as perioperative complications and survival rates that were not significantly influenced by surgery timing. One of the disadvantages of that study was the failure to include intervals longer than eight weeks.

In contrast to other studies, Habr-Gama et al.[51] showed decreases in the sphincter preservation rate for intervals longer than 12 weeks. However, these results are difficult to interpret, since patients with complete clinical response did not immediately undergo surgery. Moreover, Huntington et al.[33] reported that intervals longer than eight weeks may result in decreased sphincter preservation.

To date, no studies have conclusively demonstrated that alterations in surgical timing have significant repercussions on the choice of procedure. It is important to check the surgeon's availability to change the surgical plan and whether tools that would allow this decision (such as high-resolution magnetic resonance imaging [MRI]) are available in the pre-surgical reassessment, although there is no consensus on this subject.

Complete pathological response

Retrospective studies demonstrated that intervals greater than eight weeks after CHRT appear to present higher rates of complete pathologic response when compared with lower intervals.[37,38,41–46,54] According to some studies, maximal complete pathological response is observed between 10 and 11 weeks. Those studies also indicated that no greater benefit is observed after 11 weeks of interval.[38,40]

A more recent retrospective study confirmed that surgery performed 9–11 weeks after CHRT is associated with a greater likelihood of not finding viable tumor cells in the surgical specimen. However, in tumors that did not respond to neoadjuvant treatment, this interval also presented an increased risk of positive surgical margins and increased morbidity rate. Therefore, it suggests a limit to the benefits of postponing surgery, which may have a negative effect on the survival rate due to the anticipated tumor growth.[33]

Some randomized clinical trials indicate intervals between eight to 14 weeks as safe, with improved oncologic outcomes, local control rate, and disease-free survival.[25,30] Despite the evidence in favor, other trials have failed to demonstrate these benefits and observed a worse prognosis in postponing surgery when comparing intervals of 11–12 with intervals of six to seven weeks.[26,27]

Although a complete pathologic response is an important prognostic factor in LARC,[53] it is unlikely that postponing surgery to increase complete pathologic response alone can lead to improved survival rates.

The results of larger randomized trials ($n = 216$) that are currently underway should bring light to this issue.[23,29]

Tumor response

Some studies indicate a significant increase in the rates of tumor downstaging when using intervals of more than six to eight weeks between CHRT and surgery, with a peak between 10 and 11 weeks.[34–36,38,40,45,52] More recent clinical trials have confirmed this trend, demonstrating improvements up to 14 weeks,[25,32] while others failed to observe significant differences.[26,27]

Surgical margins

Most retrospective studies suggest that there is no increased risk of disease progression at intervals of more than eight weeks, and even at four weeks.[37,38,42,43,45,47–49,52,54] Two retrospective studies observed a significantly increased risk of positive surgical margins after the 56th and 60th day after neoadjuvant CHRT, respectively.[33,34] Caution is required when drawing inferences from these studies, since factors of poor prognosis (advanced age, comorbidities, and postoperative complications, among others) may have influenced patients in whom surgery was postponed to the "maximum". In clinical trials that assessed this outcome,[26,27] the results were not influenced by this interval, except for one study, which indicated a decrease in the rates of positivity of surgical margins.[25] It should be noted that the reduced size of the study group may have been a bias in that trial.

Perioperative morbidity and mortality

Few studies have observed significant alterations in this parameter. In fact, only two observed greater perioperative morbidity, with increased complications such as anastomotic dehiscence.[27,50] Conversely, one study observed a decrease in anastomotic and perineal complications after abdominoperineal resection at intervals averaging 10 weeks after CHRT.[47] No statistically significant differences in perioperative mortality were observed in any of the studies.

Long-term outcomes

Local recurrence rate, metastization, and disease-free survival

Transversal to almost all studies, there is little evidence that altered surgical timing impacts long-term cancer outcomes. At intervals greater than eight weeks (up to 14 weeks), increases in disease-free survival were reported by only two studies.[25,45] Another study demonstrated a decrease in local recurrence.[46] No studies observed different results regarding metastatic risk.

Preoperative treatment with chemotherapy after CHTR

An alternative option to potentiate the effects of systemic chemotherapy on LARC is to administer this treatment preoperatively, after neoadjuvant CHRT and prior to surgical treatment. The theoretical advantage of this type of treatment is the possibility of extending the interval between radiotherapy and surgery, maximizing the degree of tumor regression with active treatment and avoiding distant metastasis.

Garcia-Aguilar et al. compared a conventional neoadjuvant CHRT and surgery after 6–8 weeks with a conventional CHRT regimen followed by two, four, or six cycles of FOLFOX-6 (chemotherapeutic regimen that includes folinic acid, 5-fluorouracil, and oxaliplatin) and then surgery.[28] The interval between conventional neoadjuvant CHRT and surgery ranged from 8.5 weeks to 19.3 weeks in the group that underwent six cycles of FOLFOX-6. The results were very promising, since the groups with longer duration of treatment presented progressive increase of the complete pathological response without major difficulties of the surgical technique or risk of postoperative complications, despite the increase of fibrotic tissue. However, it remains to be ascertained whether this improvement in pathological response was due to the addition of the FOLFOX-6 cycles, due to the simple increase in the interval between CHRT and surgery, or due to both. This aspect is especially relevant, since patients who underwent systemic chemotherapy between CHRT and surgery showed some increased risk adverse effects.[9] The rapid trial that is currently being conducted may help to understand this hypothesis of treatment.[29]

Conclusion

Rectal carcinoma is one of the most relevant malignancies in the Western world. Despite its high incidence and mortality rate, there are many unanswered questions regarding optimal treatment. In addition to the conventionally accepted treatment modalities and potential future treatments, changes in the current treatment timings appear to influence treatment outcomes.

Based on the current literature, the recommended LARC treatment is neoadjuvant CHRT and subsequent surgery with total excision of the mesorectum. The interval between these two treatments appears to play an important role in disease management.

The present study suggests that intervals greater than eight weeks after neoadjuvant CHTD result in improvement of short-term outcomes such as significant increase in complete pathologic response and tumor downstaging, with no impact on perioperative mortality.

Although there is greater evidence that intervals between eight to 14 weeks are not at increased risk of disease progression, some doubts remain, since contradicting studies indicated an increased risk of surgical margins positivity and perioperative complications in those patients in whom there is no evidence of a response to neoadjuvant treatment.

Sphincter preservation does not appear to be influenced by the timings of the surgical treatment.

Conclusions about the influence of these timings on long-term outcomes such as local recurrence, disease-free survival, and metastatic risk are scarce. Only three studies demonstrated improved rates of local recurrence and disease-free survival. No changes in patient survival were demonstrated.

Based on more recent studies, the use of systemic chemotherapy during the interval between CHRT and surgical treatment may be promising, increasing the interval while performing active treatment. There appears to be improvement in complete pathological response and increase of tumor downstaging; nonetheless, further investigation is required before further conclusions can be drawn.

This review has various limitations, namely due to the heterogeneity of results. This derives mainly from the fact that the studies adopted very different intervals between CHRT and surgery, assessed different outcomes, and that most of the data were collected from retrospective studies. The clinical trials conducted to date were inconclusive or small in scale.

Although more comparable studies are necessary, this review concluded that there is a growing body of evidence to support the current practice of adopting an interval between neoadjuvant CHRT and surgical treatment superior to the six to eight weeks, which has demonstrated to safely improve short-term outcomes. However, the impact on long-term outcomes requires further study. The clinical trials that are being conducted are expected to bring some answers to these questions.

Conflicts of interest

The authors declare no conflicts of interest.

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