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Rectal cancer with a complete clinical response after neoadjuvant CRT. No immediate surgery

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One of the most controversial issues in current management of rectal cancer is the decision between immediate surgery and non-immediate surgery after complete clinical response following neoadjuvant CRT [1]. The idea of treating selective rectal cancers exclusively with radiation therapy is not new. The fact that some rectal adenocarcinomas do completely vanish with radiation therapy was already appreciated by Rider and Dukes long before modern rectal surgery was standardized [2, 3]. Before discussing what to do after a complete clinical response, one must define what a complete clinical response is. In fact, there is no unified definition of a complete clinical response of a rectal cancer treated by neoadjuvant CRT. The effects of radiation therapy (and associated chemotherapy) in a rectal cancer may vary from no significant reduction of the primary tumor to its complete disappearance. Commonly, a well-defined residual nodule or small and superficial ulceration may easily be identified by simple digital rectal examination combined with proctoscopy. These latter residual features are by no means a complete clinical response and should not be considered for non-operative approach. Full-thickness transanal excision may be an appropriate initial approach for these lesions, either as a diagnostic procedure (complete pathological response) or as an alternative treatment strategy still under investigation in clinical trials [4, 5]. The complete clinical response should be considered only in patients where there is no palpable or visible lesion, irregularity, ulcer under DRE and proctoscopy. Additional radiological studies such as MRI, ERUS or pelvic CT scans may further help identify possible residual lesion outside the rectal wall such as perirectal nodes or even mesorectal metastases. More recently, PET-CT is being investigated for its role in detecting and ruling out residual cancer in these patients [6]. Therefore, the consideration for non-immediate radical surgery in patients with rectal cancer following neoadjuvant CRT should include these patients with no clinical or radiological evidence of residual disease and those with small residual nodule proven to be complete pathological responders after a complete full-thickness transanal excision (ypT0).

One of the main arguments favoring radical surgery in these patients would be the presence of microscopic residual disease, either within the rectal wall or in perirectal nodes despite the appearance of a complete clinical response, as observed by others [7, 8]. Interestingly, radiation-induced necrosis seems to be time dependent and short intervals between CRT and surgery could have resulted in interruption of ongoing necrosis in these patients. Additionally, increased intervals between CRT and surgery has been associated with

increased tumor downstaging and complete pathological response rates [9]. A similar biological effect is observed in epidermoid anal cancer, where the rates of complete clinical response may increase significantly after stretching the interval between CRT and response assessment from 4 to 8 weeks [10]. Finally, even when microscopic residual foci may persist, the clinical relevance of these is yet undetermined. These data raises the question of when should response to neoadjuvant CRT be assessed. It seems that waiting longer than the standard recommendation of 6 weeks (at least 8 weeks, but possibly longer) from completion may actually be beneficial for these patients in terms of additional tumor downstaging and radiation-induced necrosis. Interestingly enough, even the rates of micrometastases within lymph nodes seem to be reduced after at least 8 weeks from CRT [11].

The observation of complete pathological response after neoadjuvant CRT in up to 30% raised the question of the true benefits of radical surgery in this setting after not removing a single cancer cell from the patient [12-14]. In our experience, after retrospectively reviewing the outcomes of 22 patients managed by radical surgery with no residual tumor, disease-free and overall survival was no better than the observed results after observation alone in 71 patients with complete clinical response sustained for at least 12 months after CRT completion [13]. One should not forget the significant rates of sexual, fecal incontinence, stoma requirements and urinary dysfunction associated with surgery for distal rectal cancer, which might all be unacceptable when there is no residual cancer.

But is this strategy really safe? First, analyzing 99 patients managed by observation alone after at least 12 months of sustained complete clinical response, local recurrence rates were under 7% and all could be salvaged by radical surgery, local excision or even additional brachytherapy. Interestingly, these patients had distinct patterns for local and systemic recurrences. Local recurrences were more likely to occur after prolonged follow-up periods as opposed to systemic recurrences which tended to occur earlier [15]. This could be explained by the inability of staging methods to detect microscopic systemic disease at baseline. Therefore, local failure is infrequent and commonly amenable to salvage therapy.

Still, assessment of tumor response is far from perfect, even with the aid of 3-D ERUS, new developments in MRI and high-definition PET-CT. Thus, a proportion of these patients could be erroneously considered to have complete tumor regression at initial tumor response assessment at 8 weeks from CRT completion. This would result in early tumor regrowth and a possible negative impact in survival due to a delay in definitive surgical treatment. After reviewing our own series of patients, there were 132 patients who were considered to have a complete clinical response after 8 weeks from CRT completion. However, only 99 (83%) patients sustained a complete clinical response for at least 12 months, whereas 23 (17%) developed early tumor regrowth within this 12-month period. These 23 patients were managed by radical surgery, delayed to a mean of 48 weeks between CRT and surgery. Still, there was no detrimental effect on survival of these patients managed by delayed surgery when compared to patients managed by surgery and not suspected for complete clinical response (Habr-Gama et al. Int J Radiat Oncol Biol Phys 2008; ***in press***).

In this setting, with all the available data, no immediate operation may considered a safe alternative approach for patients with rectal cancer and complete clinical response following neoadjuvant CRT. Close surveillance may allow early identification of tumor regrowth of those patients mistaken for complete tumor regression with apparent no negative influence on survival. Those patients with sustained complete clinical response are expected to develop local recurrence rates under 10%, after a significant prolonged follow-up period, which they will not be faced with the immediate surgical morbidity, urinary and sexual dysfunction and stoma requirements. Among these <10% of patients, salvage therapy will be almost always feasible. Finally, those 90% who will not develop recurrent disease will be definitively spared from unnecessary surgery.

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