Editorial

Potential value of immunoscoring in rectal cancer patients

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Rectal cancer therapy has markedly changed during the past decades with clear improvements for the patients (1). Population-based data based on registries with high validity (2,3) show that local recurrence rates can be as low as about 5% (4,5), similar to that in dedicated centers. Multidisciplinary team discussions prior to therapy initiation have likely also contributed to the improvements (5,6).

Better loco-regional staging, preferably with magnetic resonance imaging (MRI) can adequately describe whether the tumor is clear from the mesorectal fascia (MRF) and that an R0 resection thus is likely if a total mesorectal excision (TME) is done. If MRF is threatened, usually <1 mm, or cT3 mrf+, or involved, as it is in clinical stage T4 (cT4), preoperative treatment with time for down-sizing or down-staging before surgery is most often needed (1,7,8). Chemoradiotherapy is then the best documented treatment although in elderly patients, short-course radiotherapy with a delay is an attractive option (9). These tumors constitute about 10–15% of the rectal cancer patients. Many tumors less advanced than the locally advanced (cT3mrf+ or cT4s) have a risk of local recurrence even if adequate surgery is done and preoperative radiotherapy is then indicated. Since there then is no need for down-sizing/down-staging, short-course radiotherapy with immediate surgery is an attractive, convenient and well-documented treatment that reduces the risk of local recurrence by about 60% (1). These tumors, often designated locally advanced by most researchers, are best named intermediate, as for example done in the ESMO guidelines (7,8).

For early tumors, the risk of local recurrence is so small (2–5%) that radiotherapy is not indicated even if it would decrease the risk even further, since radiotherapy adds to the morbidity seen after surgery (1).

Overall survival has not improved to the same extent. The loco-regional treatments, surgery and radiotherapy have no possibilities to influence systemic disease whether already manifest at diagnosis as synchronous metastases or appearing during follow-up as metachronous metastases. Adjuvant chemotherapy is not particularly efficient and much controversy exists about whether it has any effect at all in patients pretreated with radiotherapy or chemoradiotherapy (10-13). Presently, much focus is on delivering the systemic treatment prior to the loco-regional treatment. Several trials are ongoing, among them the RAPIDO trial randomizing patients between the reference treatment chemoradiotherapy, surgery and optional adjuvant chemotherapy versus short-course radiotherapy, neo-adjuvant chemotherapy and finally surgery (14). The term “total neoadjuvant treatment, TNT” has sometimes been used to describe this most recent development.

Another trend in rectal cancer management has focused on organ preservation, i.e., to postpone surgery, potentially indefinitely in patients who respond well to chemoradiotherapy or short-course radiotherapy alone (15). If radiotherapy is indicated to loco-regionally control the disease sufficiently better than surgery alone, it is rather uncontroversial to postpone surgery if a clinical complete remission is achieved. Although some rather small distal tumors can be locally advanced since they may threaten the MRF or grow adjacent to or into the levator- or sphincter muscles, requiring preoperative therapy with a delay to surgery, most tumors requiring preoperative therapy are quite large and the probability then to achieve a durable complete remission is much smaller. Tumor size is presently

the best predictor of whether a complete clinical remission will be seen or not. In order to avoid surgery, many early tumors are thus presently treated with chemoradiotherapy. If the tumor is sensitive enough, that patient may have a clear benefit, but for most patients the additional chemoradiotherapy will only add morbidity since those patients will have both chemoradiotherapy and subsequent surgery (16).

In order to improve the outcome after rectal cancer treatments further, we need better predictors, firstly of those who will recur after adequate surgery, i.e., are at risk of having subclinical distant deposits and, secondly, of sensitivity to radiotherapy or chemoradiotherapy. The work recently published by Anitei *et al.* in *Clinical Cancer Research* (17) had the aim to determine whether tumor immune cell infiltration, as evaluated with the immunoscore methodology, could be useful as a prognostic and predictive marker in rectal cancer patients. In patients treated with surgery alone, the endpoint was risk of recurrence, either locally or systemically. In patients treated with chemoradiotherapy, the aim was to predict whether the patients will remain recurrence-free after the preoperative treatment based upon the immunoscore in the diagnostic biopsies. The results indicate that the immunoscore is both prognostic and predictive, but the strength in this is not particularly high.

In the introduction of the article, the authors refer to an assumption by many researchers that tumor progression essentially has relied upon cell autonomous processes, i.e., the genetic changes in the tumor cells. The relevance of the microenvironment has, according to the authors, been neglected. Although much knowledge how to evaluate the microenvironment, including the response of the host to the tumor has been gained during the past decade, the prognostic role of the composition of the microenvironment in colorectal cancer (CRC) has been known since at least the 1970s (18). Since then, multiple studies have revealed its prognostic impact, also in colon and rectal cancer (19-21).

In the study, a methodology named "immunoscore" was used. It was developed in a study in colon cancer (19) as a means to standardize the evaluation for routine testing and is based on the numbers of CD3+ and CD8+ lymphocytes in the center and periphery of the tumor. The use of a score that has the potential to be standardized is a strength of the study. The study with its limited number of patients, particularly in the evaluation of response after CRT, is, however, only preliminary and should be followed by a much larger validation study. The statement by the authors in the very last sentence in the discussion "an international multicenter study should now be initiated", prior to its use clinically is definitely true (22).

The need for a predictor of response to (chemo) radiotherapy is as discussed above urgently needed. This is particularly the case in early tumors where (chemo) radiation is not considered needed if major surgery is planned, but where this will be given if organ preservation is aimed at. Studies with the aim to predict outcome based upon properties of the tumor in the diagnostic biopsies are notoriously difficult, not the least depending upon the small amount of cancer cells present in the biopsies, unless "big bites" are taken. So far, no study has shown any clinically relevant predictor (23). The purpose of the diagnostic biopsy is still only to verify the cancer diagnosis. In this context, functional imaging may be methodologically easier to explore.

The performance of the immunoscore on the pretreatment biopsies in the article (17) is not possible to judge based upon limited number of patients (n=55), no prescription of what CRT was used (presumably about 50 Gy with a fluoropyrimidine) and the limited description of what constituted ypTN downstaging. An evaluation of response using either MRI pre-surgery (24) or one of the pathological tumor regression systems is likely more relevant.

While I am sceptic to that immunoscoring in the postoperative specimen will be practically valuable in the clinics to evaluate recurrence risk and in the pretreatment biopsies to predict response to CRT, I am optimistic that further studies about the interplay between the tumor cells and the environment will lead to better understanding of mechanisms of clinical value in the future. In this context, improved possibilities to measure immune reactivity in peripheral blood, beyond those that could be done using simple routinely taken tests like C-reactive protein (CRP) or the Glasgow prognostic index (25) are needed. Any new method claiming to be used clinically must be compared with what is already around, often having the advantage of being both simple and cheap.

The checkpoint PD-1 and PDL-1 inhibitors directed against the inflammatory response (26) have created greater enthusiasm for therapeutic progress than many other targeted drugs have, also in CRC. Although the first very limited series of patients with metastatic CRC treated with pembrolizumab indicated that only MSI-H tumors, where the immune reaction is more pronounced (27), responded,

the study by Anitei and co-workers (17), showing that an immune reaction in rectal cancers have prognostic information, give hope also for therapeutic attempts in rectal cancer, where MSI-H tumors virtually never are seen.

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Footnote

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