Editorial

Predicting development of distant metastases and long-term outcome of locally advanced rectal cancer treated with neoadjuvant chemotherapy and radiation

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In the last 30 years, meaningful improvements have been achieved in the treatment of locally advanced rectal cancer (LARC). In particular, the rates of local recurrences have been reduced from 30–35% to less than 10% (1). The proportion of patients that require an abdominoperineal resection has also been reduced with figures of Miles amputation now generally below 10% (2). Furthermore, organ-sparing approaches have been developed for patients achieving a major response to neoadjuvant chemoradiation potentially allowing to successfully postpone surgery in up to 20% of LARC patients treated with neoadjuvant treatment and definitively avoid it in approximately two thirds of them (3).

This substantial improvement in local control and local management has not been paralleled by results achieved in distant control. Rates of distant metastases remain indeed in the 25–30% range, not far from those reported before the wide spread use of total mesorectal excision (TME) surgery and routine combined modality strategies (4,5). This may depend on lack of chemotherapy regimens efficacious on micrometastatic disease as well as on inadequate use of systemic chemotherapy due to the long running controversy on the benefit of adjuvant chemotherapy in LARC and suboptimal compliance.

Total neoadjuvant therapy (TNT) that allows optimal delivery of adequate doses of systemic chemotherapy appears to represent an important step forward but even with this strategy distant metastases occur in 20% of patients already at 3 years (6,7). The ability to predict the development of distant metastases and overall survival (OS) in LARC patients treated with neoadjuvant chemoradiotherapy (CTRT) has therefore a major clinical relevance. It could indeed allow to modulate the use of systemic chemotherapy (either maintenance between the end of CTRT and surgery or adjuvant chemotherapy), its duration and the choice of the most appropriate regimen. Information on the risk of distant failure could also drive less or more intense follow-up programs. This latter aspect is particularly important for liver metastases (LM) that may be curatively resected.

In this issue of *Annals of Translational Medicine*, Zhou and coauthors (8) report on the development of a nomogram that predicts the risk of LM and survival in LARC treated with neoadjuvant CT or CTRT. Data (n=302 patients) from FORWARC, a randomized clinical trial of neoadjuvant therapy for LARC, which compared modified infusional fluorouracil, leucovorin and oxaliplatin (mFOLFOX6) with or without radiotherapy with fluorouracil and radiotherapy (9), were used to estimate the risk of LM after surgery based on a combination of clinicopathologic variables. Data from a prospective cohort of 100 consecutive LARC patients from the same institution were used as an external validation set. The best model for liver disease free survival (LDFS) included the following predictors: hepatitis B virus (HBV) infection, anemia, number of lymph nodes in the pathological specimen, tumor nodule, and ypT stage.

The most predictive model for OS was based on predictors similar to those for LDFS: mesorectal fascia (MRF) involvement, ypN, pathological differentiation, tumor nodule and neural invasion.

Nomograms models based on recognized prognostic features have been developed for several tumors in the attempt to enhance outcome prediction. These statistically based tools provide the overall probability of a specific clinical outcome for an individual patient rather than a generic risk group. Previous studies in rectal cancer suggest improved predictive accuracy using this approach (10,11), but did not specifically focus on LM estimation. Zhou and coauthors have originated a nomogram that predicts LM after neoadjuvant therapy and surgery based on a post cohort study of a randomized trial and comprehends both factors included in common clinical staging systems and others parameters possibly influencing biological response and compliance to treatment. This model offers an individualized risk evaluation that is easily understandable by physicians and patients. The inclusion of HBV infection in the model is an added value considering the high prevalence of this infection in China.

In this study, only LM have been analyzed. Although lung, peritoneal and lymph nodes metastases are also important sites of recurrence in LARC (lung 9–10%, locoregional sites including lymph nodes 5–6%, peritoneum <1%) (4-7), liver disease remains the main site of distant failure and has a particular clinical importance given the possibility of curative liver resection in at least one quarter of patients.

Response to preoperative chemoradiation and pathologic tumor stage post-neoadjuvant treatment are largely used to predict prognosis and inform adjuvant treatment decisions in LARC patients treated with preoperative CTRT and surgery. Correlations between pathological complete response (pCR), primary tumor downstaging or tumor regression grade (TRG) and long term outcome have indeed been shown. However, a pooled analysis of 22 randomized trials has demonstrated that pCR is not a surrogate endpoint for survival (12). Other studies have shown that pCR is not a predictive factor for improved survival (13). Additionally, a randomized controlled trial found that TRG has no prognostic impact on DFS (14). Therefore, DFS and distant metastasis free survival cannot be predicted by local response only.

In the model reported here, HBV infection and hemoglobin levels appear to be strong negative predictors of LM. This suggests that host conditions as well as liver microenvironment might be more important than tumor stage in determining the risk of liver recurrence.

The growth of LM may be sustained by immune-modulatory and angiogenic activity guided by the primary tumor upon progression (15). Liver microenvironment may affect the homing and nesting of circulating tumor cells. The metastatic propensity of tumor cells is both intrinsic to the tumor cells and guided by the local environmental status of metastatic sites (16). Studies have indicated that pathological features of primary colorectal cancers were not modified by viral hepatitis; whether changes in liver immune responses influence liver migration of colorectal cancer cells in HBV infected patients remains uncertain. The liver includes a considerable amount of immune cells, particularly T cells and natural killer cells, which can successfully eliminate metastatic cancer cells, demonstrating that variations in liver-associated immunity may cooperate in hindering hepatic metastases (16). In HBV-positive liver cancer, HBV replication has been shown to enhance immunocytes cytotoxicity during chronic HBV infection (17). The high rate of HBV infected patients in the FORWARC cohort (HBV infected: 28.5%) could thus possibly explain also the lower rate of LM compared to previously reported data (25–30% *vs.* 7–9%). As to the influence of anemia it is intriguing to speculate that a lower number of red blood cells could affect the adherence of tumor cells to platelets and the formation of tumor clots and therefore reduce transit to the liver through the portal vein (18). Moreover, in the context of a proinflammatory microenvironment enriched of macrophages and increased tumor vasculature, red blood cells and hemoglobin could also stimulate tumor cell proliferation and remodel tumor stroma (19).

The apparent lack of prognostic value of yp stage is somehow surprising. Nevertheless, evidence has accumulated about the effect of distinct pathological features, which could considerably affect the prognosis of colorectal cancer patients. Currently, detection of tumor deposits has a limited position in the tumor node metastasis (TNM) staging system for colorectal cancer. Nevertheless, a recent analysis from Surveillance, Epidemiology and End Results (SEER) database proposed nodal reclassification incorporating tumor deposits in combination with tumor stage based on the strong prognostic impact on cancer specific survival (20).

Development of reliable tools to predict distant metastases in LARC patients after neoadjuvant treatment and surgery is clinically important and may inform decision

on adjuvant treatment and follow-up. The proposed nomogram represents a valuable instrument at this regard. This could be further developed and optimized including additional parameters (newer molecular markers, extramural venous invasion, immunoscore). Circulating tumor DNA (ctDNA) assessment will probably also help to optimize risk prediction and patient stratification for adjuvant treatment. Latest studies analyzing ctDNA in patients with solid tumors suggest in fact the potential to accurately predict and detect earlier relapse, allowing treatment approaches that may effectively improve patient outcomes.

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