Editorial

Tumor deposits in stage III colon cancer

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Colorectal cancer (CRC) remains one of the primary causes of cancer mortality worldwide (1). The tumor node metastasis (TNM) classification, which is based on tumor extent, lymph node involvement, and presence of distant metastasis, is still the most commonly used approach to inform patient prognostication and decision making in clinical management. This classification helps to stratify patients into different risk levels of cancer recurrence and survival after curative resection, and guides the appropriate use of systemic adjuvant therapy. Systemic adjuvant therapy can improve the overall survival of patients with stage III colon cancer by around 3–5%, but is associated with a risk of significant side effects and a small risk of death (2,3). Better stratification is therefore needed to distinguish between patients at higher risk of recurrence who are more likely to benefit from adjuvant therapy, and those at lower risk of recurrence who have a better chance of cure by surgery without adjuvant therapy.

Tumor deposits (TD) have been defined by the current TNM classification 8th edition, published in 2017, as isolated foci of carcinoma in the pericolic and mesenteric fat tissue away from the leading edge of the primary tumor, with no sign of residual lymph nodes or identifiable vessels or neural structures (4). Historically, TD were first described by Gabriel *et al.* in 1935 (5) and were first incorporated in the 5th edition of the TNM classification system, published in 1997 (6). Since then, the precise definition of TD has changed from size-based in the 5th edition (nodules >3 mm were counted as positive lymph nodes, whereas nodules ≤3 mm were considered as TD and included in the T category), to shape-based in the 6th edition in 2002 (TD were defined as a lack of smooth shape and evidence of nodal architecture) (7). In the 7th edition, published in 2010, TD was defined by identifying features of residual lymph node tissue instead of using a specific size- or shape-based rule, and isolated tumor foci with no evidence of remaining lymph node tissue, regardless of size or shape, were considered to be TD (8). A separate lymph node subcategory of N1c for TD without concurrent positive lymph nodes has been introduced since the 7th edition (9). However, it is not clear if the N1c lymph node subcategory is equivalent to lymph node metastasis in both the biological and prognostic senses. Biologically, the origins of TD remain controversial. Although a nodule diagnosed as TD may be merely a thoroughly infiltrated lymph node in which no normal lymphatic tissue remains, recent studies have reported strong correlations between the presence of TD and vascular invasion (10,11). Prognostically, several reports have focused on the outcome of patients with N1c CRC and have identified N1c as a poor prognostic factor; however, these reports only included small numbers of patients (12-14).

In this issue of *Disease of the Colon and Rectum*, Wong-Chong *et al.* addressed the clinical impact of TD in a large population-based study of patients with stage III colon cancer using the United States National Cancer Database (15). They divided all patients with stage III colon cancer into three subgroups: lymph node metastasis-positive with TD (LN+TD+), lymph node metastasis-positive without TD (LN+TD–), and lymph node metastasis-negative with TD (LN–TD+). Their study elucidated the clinical significance of TD in a large number of current stage III patients. First, they showed that LN–TD+ (N1c) patients had a similar overall prognosis to LN+TD–

patients. In addition, LN–TD+ patients, as well as LN+TD+ and LN+TD– patients, benefited from adjuvant systemic therapy. Although it is difficult to determine if TD should be considered as lymph node metastasis or satellite tumor nodules for the purpose of cancer staging, these results suggest that TD should clinically be considered as lymph node metastasis. Using the current N category, pathologists and clinicians can simplify the TNM staging system and make suitable suggestions for patients' postoperative treatment. Second, representative randomized controlled trials of adjuvant therapy did not consider TD in any subset analyses (16,17), and Wong-Chong *et al.*'s work demonstrated the important survival benefit of adjuvant therapy in N1c patients, indicating that adjuvant systemic therapy can improve survival in N1c patients, in whom adjuvant therapy is currently underutilized and delayed. Third, they showed that LN+TD+ patients had lower 5-year overall survival compared with either LN+TD– or LN–TD+ patients (46.0%, 63.4%, and 61.9%, respectively). In addition, LN+TD+ patients had a poorer prognosis regardless of the number of lymph node metastases. These results demonstrate an additive effect of TD in lymph node-positive CRC patients. The current TNM classification ignores the coexistence of TD in patients already classified as N1 due to involved lymph nodes. A recent systematic review confirmed that TD was independently associated with lower overall and disease-free survival, based on recently published survival data (18). This adverse association persisted even in patients with positive lymph nodes, strongly suggesting that TD should not just be included in the N category for staging purposes, because of its separate and additive impacts on prognosis (19).

The concept of TD in CRC is clinically significant. Regarding the frequency of TD, a recent systematic review showed a median incidence of TD of 21.3% (10.2–44.2%) (20). The current study by Wong-Chong *et al.* demonstrated a similar prevalence of 25% in patients with stage III colon cancer. However, outcome data for TD have not yet been estimated accurately due to different definitions, resulting in stage migration and thus producing variable results. Further evidence is needed to elucidate the impact of TD as defined in the most recent TNM classification. Poor inter-observer agreement caused by subjective histologic features of residual lymph nodes also needs to be resolved in the current definition of TD (21).

In conclusion, Wong-Chong *et al.* revealed that it was feasible to consider TD as positive lymph nodes in the N category for evaluating the prognoses of CRC patients. There may be scope for improving the prognosis of N1c patients by the prompt and appropriate administration of adjuvant therapy. Furthermore, given the additional significant practical impact of TD on patient prognosis, TD must be taken into consideration when applying specific substaging in stage III colon cancer in future editions of TNM staging.

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