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Targeted lymph node evaluation in colorectal cancer: A decade of progress!

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Systemic chemotherapy has been shown to improve survival in stage III and stage IV colon cancer (CC), however, current recommendations1 do not support the routine use of adjuvant chemotherapy in node negative CC (stage II). Despite this, over 20% of stage II CC recur, and recent studies have demonstrated2 that some subsets of stage II CC have a lower median survival than stage III CC. This may indicate a high risk group of stage II CC that would benefit from adjuvant chemotherapy. Since lymph node (LN) status is one of the most important prognostic factors, it is possible that the recurrence in stage II CC may be explained by the failure to detect clinically and biologically significant nodal micrometastases (MM). Insufficient nodal resection or pathological evaluation, LN sampling error, and limitations of conventional hematoxylin and eosin (H&E)-stained evaluation are all significant limitations of standard pathological staging of CC. LN's from a resected specimen are typically identified by a combination of visualization and palpation although as many as 70% of LN are <5mm in diameter, and may be the only ones that contain metastases.3 Fat clearance techniques using organic solvents have been used resulting in the identification of more nodal metastases4 but these are time consuming and cumbersome and therefore not widely utilized in clinical practice.

Other techniques have also been developed to improve the identification of MM, such as multi-level sectioning, cytokeratin immunohistochemistry (CK-IHC) and reverse transcriptase-polymerase chain reaction (qRT) but there prognostic significance is unclear 5–10. In a recent metaanalysis,11 although MM were identified in 31.2% and 44% of patients by CK-IHC and qRT negative by H&E, survival was only impacted by qRT suggesting that the biologic and prognostic value of MM requires further investigation. The development of recurrence in node-negative patients could also be attributed to residual MM because of inadequate lymphadenectomy. Pooled analyses of data from randomized trials12,13 have demonstrated a strong correlation between survival and the number of lymph nodes examined, independent of other known prognostic factors.

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Last year the National Quality Forum (NQF) in conjunction with the Commission on Cancer, the American Society of Clinical Oncology, the American College of Surgeons and the National Comprehensive Cancer Network devoted a substantial effort to improve the quality of CC care in the United States. This culminated in the endorsement of the 12 LN minimum as a proxy measure of quality. Unfortunately, while the prognostic importance of LN status is undisputed, there continues to be debate about the number of LN's needed for adequate evaluation, techniques for sampling and assessment of LN's and the integration of pathologic and molecular features of the primary tumor to improve the selection of patients for chemotherapy. More specific methods for nodal evaluation are therefore needed.

Targeted nodal evaluation was originally described by Morton et al14 to improve staging accuracy in melanoma and reduce the morbidity of lymphadenectomies in node negative patients. This paradigm is based on the premise that lymphatic drainage from a primary organ site occurs in an orderly and progressive fashion. The sentinel node (SN) is the first node(***s***) to receive lymphatic drainage from a primary anatomic site, and is therefore the most likely node(***s***) to harbor a metastasis and is representative of the regional lymphatic basin. Lymphatic mapping and sentinel node biopsy (LM/SNB) is now widely accepted as the standard of care for staging melanoma and breast cancer. Over a decade ago15 we applied targeted nodal evaluation to colorectal cancer (CRC) specifically to determine whether staging accuracy could be improved. Unlike melanoma however, the procedure was not intended to limit LN resection since the morbidity of a colectomy is not impacted by the number of LN's removed but rather to determine whether focused analysis on a limited number of LN's could improve staging accuracy. Since our original report several techniques of LM have been described in CRC with a wide variation in sensitivity and accuracy.16–22 This has been attributed to differences in technique, experience, patient selection and inconsistent definitions of micrometastases (MM) and upstaging.

The AJCC and the UICC distinguishes MM from isolated tumor cells (ITC's) based on size and method of detection. MM identified by H&E between 0.2 and 2 mm are classified as N1mi while ITC's and tumor cell clusters up to 0.2mm are considered N0 i+ (IHC) or NO mol+ (qRT) depending on the method used 23,24. These stricter definitions were recently applied to two prospective multicenter trials with similar results. 21,22 Stringent pathologic criteria were also used whereby tumor cells identified by IHC without characteristic tumor morphology were not considered positive. Targeted analysis of the SN using IHC upstaged 11% of patients and isolated tumor cells/clusters were found in 23% of patients with stage II CC that would not have been detected by conventional methods. Translational molecular studies also identified MM within the SN via qRT21 and identified potential factors in facilitating these MM using RNA and DNA markers. At a mean follow up of 25 months there were no recurrences in patients whose SN was negative by H&E/IHC and qRT suggesting that this may represent a low risk group cured by surgery alone. However since the follow up was relatively short and many patients received chemotherapy it is unclear whether the presence of MM represents a high risk group.

A larger prospective multicenter trial supported by the NCI (2RO1CA090848) will address whether the presence of MM represents a high risk group in the absence of chemotherapy. This trial will also integrate primary tumor characteristics and gene signatures to develop a

more comprehensive staging system since it is likely that some patients may be at high risk for recurrence regardless of the MM environment. Targeted nodal in CRC provides an elegant way of performing focused analysis on a limited number of LN's improving staging accuracy. It will however continue to be investigational until the biologic and prognostic role of MM in CRC is better defined.

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