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Lymphatic spread, nodal count and the extent of lymphadenectomy in cancer of the colon

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ABSTRACT

In colon cancer, the biological significance of lymphatic tumour spread remains a matter of debate, which impacts on related questions such as the ideal extent of lymphadenectomy and the prognostic significance of lymph node counts. Several lines of evidence suggest that metastasis to locoregional nodes occurs early and is a stochastic, rather than a stepwise phenomenon, and in essence reflects the tumour–host–metastasis relationship. Not surprisingly, therefore, several clinical trials failed to identify a survival benefit from extensive lymphadenectomy compared to standard resection. The recently described complete mesocolic excision technique, which aims to improve survival by maximizing nodal clearance, should be subjected to a prospective randomized trial.

There has been a fairly consistent and intriguing relation between nodal counts and survival in colon cancer. Therapeutic effects of more extensive removal of invaded nodes seem an unlikely explanation for the observed association. Similarly, several findings argue against stage migration as the only or even the most important explanation. The available literature shows an extensive array of factors confounding the nodal count–survival relationship, which are correlated to the patient's clinical characteristics, pathology variables, and factors relating to the individual (treating surgeon and pathologist) and institutional healthcare levels. More research into the biology of nodal spread and the nodal count–survival relationship is indicated and may have important implications for therapy such as the further introduction of minimally invasive surgery and the identification of novel and potentially modifiable factors impacting on both nodal counts and survival.

Introduction

Colon cancer (CC) is the third most common cancer in both men and women in the United States.[1] Surgery is the mainstay of treatment of non-metastatic CC. As in many solid tumours, the presence of nodal cancer spread is one of the most powerful prognostic variables.[2] The surgical resection specimen encompasses an area of bowel mesentery, and depending on tumour characteristics, surgical technique, and effort of the pathologist a varying number of lymph nodes is identified and analyzed for the presence of metastatic spread. During the past decade, controversy has arisen regarding the prognostic significance of the number of nodes that is harvested from a resection specimen. Notwithstanding the uncertainties that persist, many professional bodies have put forward a minimal number of nodes to be analyzed as an indicator of quality care. In parallel, the biological significance of nodal spread in CC and, therefore, the therapeutic as opposed to a merely diagnostic value of lymph node removal remain undefined. This uncertainty impacts on the possible merits of recent advances in surgical management of CC, which include minimalist approaches such as sentinel node detection as well as maximalist techniques exemplified by total or complete mesocolic excision (CME).[3,4] Here, we reviewed the biological significance of nodal metastasis in CC and discuss the clinical relevance of nodal counts, lymph node ratio, and extent of lymphadenectomy.

Methods

A comprehensive search of relevant articles in PubMed and Science Citation Index Expanded was performed. This search was done for the last time on 1 May 2013 using the search terms colon, cancer, neoplasia, tumour, tumour, adenocarcinoma, lymph node, nodal count, lymphadenectomy, prognosis, prognostic, predictive, survival, mortality and confounding variables in various combinations.

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The reference list of identified articles was searched for further relevant studies. Exclusion or inclusion of a given study was based on its quality, relevance and uniqueness.

Biological significance of nodal spread in CC

On the one hand, the presence of lymph node metastasis (LNM) is a major prognosticator in CC. On the other hand, distant metastasis (DM) is the main cause of disease-specific death, which poses the question of how LNM relates to DM and, thus, survival. Two mechanistic models have been proposed in relation to the biological significance of LNM in epithelial cancer. Unfortunately, both are largely derived from indirect evidence. In the first model, LNM precedes DM, and invaded nodes are regarded as temporary 'barriers' or 'incubators' that eventually will seed cancer cells further down the lymphatic chain and/or into the systemic circulation.[5] Assuming this scenario is real, efforts at removing a maximal number of (possibly) invaded nodes may prevent further tumour spread and result in a survival benefit. This 'stepwise' cancer spread model championed by Halsted resulted in extensive, mutilating surgery in an effort to remove a maximal amount of nodal tissue.[6] In 1980, Fisher proposed an alternative model of breast cancer metastasis. In this parallel progression model, DM is considered to occur very early in the natural history of the disease. Data from disease courses, tumour growth rates, molecular and genetic analyses of primary and disseminated tumour cells (DTC), and clinical trials overwhelmingly favour the parallel progression model. In this model, LNM is seen as a marker of the biological behaviour and malignant potential of the disease, and efforts to remove affected nodes will not impact on survival.

In parallel, the biology of cancer is increasingly conceptualized as a tumour-host-metastasis ecosystem, which consists of early onset, continuous, and bidirectional signalling between a primary and its metastatic sites;[7] the basis of this concept was already proposed by Paget in 1889 as the 'seed and soil' hypothesis.[8] This site specificity was recently shown to modulate lymphatic tumour spread. Hirakawa and colleagues studied tumour-associated lymphangiogenesis in a transgenic mouse model overexpressing vascular endothelial growth factor (VEGF)-A subjected to chemical skin carcinogenesis.[9] They found that VEGF-A overexpressing tumours induced lymphangiogenesis in sentinel nodes even before metastasis occurred, suggesting that primary tumours prepare their future LNM by facilitating transport to sentinel nodes. Fig. 1 illustrates the participation of locoregional lymph nodes within the cellular and molecular communication associated with the ecosystem of metastatic CC.

Several lines of evidence support the concept of parallel progression in CC, characterized by cancer cell dissemination from early stages in tumour development. First, circulating tumour cells in the peripheral blood of colorectal cancer have been found in every stage of disease, independently of methods and marker(s) used.[10] In a recent meta-analysis, molecular detection of tumour cells in regional nodes was found to predict disease recurrence and worse survival in node negative colorectal cancer.[11] Most of the included studies were retrospective, however, and considerable variation existed in analytical protocol. An analysis of 312 patients with node negative CC found DTCs in lymph nodes in 16%, 52%, and 71% of patients with stage pT1, pT2, and pT3, respectively; the presence of isolated tumour cells (ITC) in regional nodes was associated with a significantly higher risk of cancer relapse.[12] Second, the estimated growth rates of primary CC and liver metastases are comparable.[13] Given the average time frame between resection of the primary and the occurrence of metastatic disease in CC, and the occurrence of synchronous metastases, the growth rate of metastases would need to be much higher if the linear progression model would be correct. Third, genetic analysis at the chromosomal, genomic, and DNA level has demonstrated a striking disparity between primary CC, DTCs, and established metastases, suggesting early dissemination of genetically less-advanced clones.[14] Finally, the linear, stepwise progression model of lymphatic spread is incompatible with the observation that (1) the number of invaded nodes is of greater prognostic significance then their exact location in the mesentery; and (2) the location of the first draining node when using sentinel mapping techniques is unpredictable and often at a considerable distance from the primary.[15,16]

Taken together, these data suggest that lymphatic spread in CC is a stochastic rather than a stepwise phenomenon, and may occur early during tumour progression. Nodal positivity reflects the tumour–host relationship and thus the biological behaviour of the disease.

Node counts and survival

Over the past decade, numerous clinical studies have reported a positive correlation between survival and the lymph node count (LNC), i.e., the number of pathologically evaluated lymph nodes.[17–22] Several explanations have been put forward to explain this observation: stage migration, therapeutic effects of lymphadenectomy, and confounding by other clinicopathological factors.

Stage migration

The underlying mechanism behind the association between LNC and survival is often attributed to stage migration, since a more extensive lymph node evaluation increases the detection rate of node-positive disease. Consequently, more node-positive patients will receive chemotherapy and thus will show better overall survival (Will Rogers phenomenon).[23] Therefore, many professional bodies have set a benchmark of at least 12 lymph nodes to be sampled as a measure of the quality of CC care.[24] However, several arguments may be raised that challenge the role of stage migration to explain the observed correlation between LNC and survival.

First, the relationship between LNC, nodal positivity rate, and survival from population-based studies is far from consistent (Table 1).[21,25–29] Of note, interpretation of data from population registries should account for the fact that in many of these studies low LNCs were reported. In a retrospective multicentre trial, Prandi and colleagues analyzed 1613 Dukes C CC patients and found that survival and the number of positive nodes was not related to the LNC.[25] Recently, Porter et al.[29] published their five years' observations of 1,583 CC stage I-III patients from the province of Nova Scotia in Canada. Similarly, despite increased LNC over time, no significant change in the node positivity rate was encountered, and increased LNC did not result in improved survival. Wong et al. retrospectively reviewed the correlation between hospitals' LNC and survival as well as staging based on 30,625 stage 0-III CC patients aged 65–99 years from the Surveillance, Epidemiology and End Results (SEER) database (1995–2005).[27] Patients who received preoperative radiation therapy were excluded. They found that a greater LNC did not result in a higher node positivity rate. However, at a patient level, examination of 12 or more lymph nodes was associated with improved survival. Likewise, a recently published cohort study by Parsons and co-workers[21] using 86,394 CC patients older than 18 years without preoperative irradiation from the SEER program (1988–2008) demonstrated that increased LNC during the past two decades was not associated with a substantial increase in lymph node positivity. However, stage I through IV patients with high levels of LNCs experienced a significantly lower hazard of death. Bui et al.[26] retrospectively evaluated the relationship