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The detection and role of lymphatic and blood vessel invasion in predicting survival in patients with node negative operable primary colorectal cancer

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Abstract

Although vascular invasion in colorectal cancer has been recognised since 1938, detection methods and results remain inconsistent. Vascular invasion is currently an independent prognostic factor in colorectal cancer influencing disease progression and survival. The vascular system consists of three components, arterial, venous and lymphatic vessels, all of which can be invaded but accurate distinction between the components remains difficult with routine staining techniques. Even though higher detection rates with elastica staining, for large vessel invasion, and recent techniques for immunohistochemistry for small vessel invasion, have been reported, a standardised method of detection has not been agreed upon which is reflected in the variability of published results. As a result of the Bowel Cancer Screening Programme in the UK it will be necessary to attempt to identify and stratify patients better, to be able to handle the stage migration to early node negative colorectal cancer. At present up to a third of patients, with node-negative colorectal cancer on conventional histopathological analysis, ultimately die of recurrent disease. It is therefore important to develop and standardised methods to identify lymphatic and blood vessel invasion which will influence ultimate survival. The present review summarises the current status of detection methods for these components of vascular invasion.

Keywords: Colorectal cancer; Detection; Lymphatic invasion; Blood vessel invasion; Prognosis

1. Introduction

Colorectal cancer represents a leading cause of cancer-related deaths in the western world and is by far the most

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common malignancy of the gastrointestinal tract [1]. Colorectal cancer forms part of a heterogeneous group of tumours that exhibit different clinicopathological features with different prognostic values, so despite the availability of multiple treatment options, the optimal management of colorectal cancer remains complex [2].

Pathological staging is currently the most accurate predictor of prognosis in colorectal cancer. Both of the commonly used staging systems for colorectal cancer (Dukes and TNM) depend upon the degree of tumour spread through the bowel wall and the number of lymph nodes containing metastatic tumour deposits and serve as a benchmark for predicting the likelihood of five-year survival [3]. The principle cause of death in colorectal cancer is metastatic disease, thus the presence of metastatic tumour in regional lymph nodes is currently considered the most significant indicator of overall survival and possible benefit to adjuvant chemotherapy [4].

Colorectal cancer disseminates as invasive tumour cells that can either enter the lymphatic system to be transported to regional lymph nodes, or enter into the blood vasculature, where they are transported in vessels of the circulatory system to other organs. Tumour cells in the regional lymph nodes can die, remain dormant, proliferate or pass through the node. Proliferation results in the formation of lymph node metastases, which can seed further metastatic tumour cells into the efferent lymphatics to form metastases in lymph nodes higher up in the lymphatic drainage, or ultimately enter the blood via the thoracic duct. Thus two routes exist by which tumours cells can ultimately reach vital organs like lung or liver; either directly via the blood circulatory system or indirectly via the lymphatic system before entering the blood circulatory system [5,6].

Despite the fact that histopathological analysis of lymph nodes appears central to all colorectal cancer staging paradigms, its prognostic and predictive value is limited, as about 30% of patients with histopathology-negative lymph nodes (pN0) die from metastatic disease [7]. Hence this paradigm underestimates the presence of metastases. Thus the heterogeneity of colorectal cancer needs to be addressed by adding additional prognostic factors [8].

This is particularly applicable with the introduction of the Bowel Cancer Screening Programme in the UK, which will result in at least 70% of cancer patients treated having node-negative disease. A trend towards earlier stage and less advanced disease has been observed, with males showing significant increases in TNM stage I and corresponding decreases in TNM stage III disease [9]. Ricciardi and coworkers reported that lymph node metastases were not as common in early stage colorectal cancers, occurring in 8% of T1 tumours and up to 18.5% of T2 tumours, leading to an increased subgroup of histopathology-negative lymph nodes (pN0) patients [10]. According to Horgan and McMillan the rising incidence of early node negative colorectal cancer underlines the necessity to better identify and stratify patients with colorectal cancer [11].

Established poor prognostic features for node negative colorectal cancer, include tumour perforation or obstruction at presentation, T4 level of invasion, poor differentiation, lymphatic and blood vessel invasion and inadequate node sampling [12]. Of these, vascular invasion is a biological manifestation of aggressive behaviour in colorectal cancer and has been widely acknowledged as a useful independent pathological indicator for predicting prognosis, as well as a good index to guide postoperative therapy. Thus patients with vascular invasion usually have a greater likelihood of disease progression and poorer prognosis [13–15]. In studies evaluating early colorectal cancer, vascular invasion appears to play an important role in predicting recurrence and prognosis [16–18] Indeed, vascular invasion may be understood as the first access of tumour cells into vessels via the lymphatic or blood stream and represent crucial steps in the formation of micro-metastases and eventually macroscopic tumour growth at a secondary site [5].

As lymphatic vessel invasion (LI) and blood vessel invasion (BVI) are crucial for tumour dissemination, they correlate with recurrence and survival in cancer [16]. The lymphatic system is one of the first pathways for tumour cell dissemination, due to loose epithelial junctions and the absence of a basement membrane [6]. Furthermore the high internal pressure within tumours leads to the passive flow of interstitial fluid with tumour cells away from the tumour into the draining lymphatic vessels [19]. According to Carter arterial pulsations can also enhance lymph flow [20]. Indeed, metastases via the lymphatic system in addition to haematogenous dissemination contribute to the systematic spread of tumour [5]. Tumour invasion to the vascular system is generally accepted as the first step in the development of metastases in malignant solid tumours [16].

Currently lymphatic invasion is grouped together with capillary invasion as small vessel involvement, designated lymphovascular invasion. Large vessel involvement includes venous invasion [21]. Nevertheless, despite the anatomical differences, these separate entities are almost routinely reported as a single entity. Recently there has been increasing interest defining these components separately [16,22,23]. Therefore, in order to rationalise the evidence between lymphatic and blood vessel invasion and the outcome in patients with node negative colorectal cancer, a systematic review was carried out. The aim of the present review was to examine the prognostic significance of the components; lymphatic invasion (LI), blood vessel invasion (BVI) and to comment on approaches to improve detection with special emphasis on node negative disease.

2. Methods

A systematic review of published literature was undertaken with the role of lymphatic and blood vessel invasion in predicting outcome (recurrence, cancer specific and overall