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The role of perineural invasion in predicting survival in patients with primary operable colorectal cancer: A systematic review

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ABSTRACT

Perineural invasion is a clear route for cancer cell spread however, the role of nerves in cancer progression is relatively unknown. Recent work would suggest that nerves can actively infiltrate the tumour microenvironment and stimulate cancer cell growth. Therefore, the aim of the present study was to systematically review the identification and associations of perineural invasion and survival in patients with primary operable colorectal cancer.

From initial search results of 912 articles, 38 studies were selected. Using H&E stains; five studies including 1835 patients reported on survival stratified by perineural invasion in colon cancer with weighted average detection rates of 26%; eleven studies including 3837 patients reported on rectal cancer with weighted average detection rates of 25% and; sixteen studies including 9145 patients reported on survival stratified by perineural invasion in colorectal cancer with weighted average detection rates of 17%. Using special techniques (S100), six studies including 1458 patients reported on the identification of perineural invasion in colorectal cancer. In comparison to H&E staining alone, the use of immunohistochemistry with S100 increased the detection of perineural invasion to approximately 70%. However, those studies did not examine the relationship with outcomes, so further research is required to establish the clinical significance of perineural invasion detected by immunohistochemistry.

In conclusion, perineural invasion deserves special attention for improved prognostic stratification in patients with colorectal cancer. Further work is required to standardise pathology assessment and reporting of perineural invasion, in particular its definition, use of special stains and routine inclusion in pathology practice. Reliable assessment is required for investigations into mechanisms of perineural invasion, its role tumour spread and prognostic value.

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1. Introduction

Colorectal cancer is a major cause of both cancer incidence and mortality (Siegel et al., 2014). Currently, Tumour-Node-Metastasis (TNM) staging is considered the most robust predictor of outcome of patients with colorectal carcinoma but is less accurate in early stage disease. Thus supplemental risk factors are required to allow selection of patients who may benefit from adjuvant treatment (Horgan and McMillan, 2010).

Currently the indication for adjuvant therapy for patients with stage II disease is based on the presence of at least one of six clinical and pathological high risk factors;poor differentiation, emergency surgery, fewer than 12 examined lymph nodes, the presence of extramural vascular invasion, perforation or a pT4 tumour (Benson et al., 2004). However, additional features, such as perineural invasion and the presence of tumour budding are recognised risk factors that do not yet influence treatment decisions. As such, perineural invasion has been included in the TNM Supplement for colorectal cancer since 2001(Compton, 2003). Perineural invasion is also identified as a site- specific prognostic factor by the American Joint Committee on Cancer (AJCC) Staging Manual (7th edition) and a high risk factor for recurrence under the National Comprehensive Cancer Network (NCCN) guidelines. Perineural invasion is included in the Royal College of Pathologists dataset (UK) to be reported as microscopic non-core data for colorectal cancer (Loughrey et al., 2014).

Metastatic disease is the principle cause of death in colorectal cancer, tumour dissemination via blood and lymphatic vessels are accepted as the dominant routes of malignant spread (Valastyan and Weinberg, 2011). However, tumour spread via nerves is plausible as an alternative route of spread and can therefore influence possible treatment prevention.

Perineural invasion has recently emerged as a key pathologic feature of several common solid cancers, including pancreas, prostate, biliary tract, and stomach. Neoplastic cells in perineural spaces may not be removed during tumour resection, and thus may result in local recurrence (Marchesi et al., 2010). Perineural invasion in colorectal cancer has been reported as an independent prognostic factor (Betge and Langner, 2011; Liebig et al., 2009a; Pagès et al., 2005) however, is not always assessed and reported. Problems with the detection of perineural invasion such as the presence of inflammatory cells, mucinous carcinoma and microscopic foci of perineural invasion can hinder consistent reporting. Presently, the clinical significance of perineural invasion remains unclear.

The aim of the present study was therefore to systematically review the identification of perineural invasion and associations with clinopathological features and survival in patients with primary operable colorectal cancer.

2. Methods

A systematic review of the published literature on perineural invasion in colorectal cancer was undertaken. In addition to methods of assessment, outcomes of interest were relationships with other clinical and pathological factors and cancer outcomes (cancer-specific survival/overall survival).

Studies were identified via a literature search of the electronic databases the US National Library of Medicine (MEDLINE), the Excerpta Medical database (EMBASE), the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts and Reviews (DARE) between 1984 and 2015 using the key words: perineural invasion; nerve; colon/rectal cancer and prognosis (last search was updated on December 3; 2015).

For inclusion, studies had to meet the following criteria: (a) perineural invasion was assessed in surgically resected primary colon and/or rectal tumours, and (b) the relationship between perineural invasion and survival was investigated in primary operable disease, and the results were published as a full paper. Studies that only reported perineural invasion as an incidental finding were excluded.

The title and abstract of each identified study was examined for relevance. Full text was obtained for all potentially relevant studies. Studies that examined the prognostic value of perineural invasion in colon and/or rectal cancer were included while studies relating to duplicate datasets, studies not available in English language and those published only in abstract form were excluded. Studies in which sample size was less than 75 patients and the median/mean follow-up was less than 3 years were also excluded. The bibliographies of all included articles were subsequently hand searched to identify any additional studies. Studies were selected after review by the author (HvW) or if there was doubt with another co-author (DCM).

Study heterogeneity precluded a meaningful meta-analysis and the results of the review are presented in descriptive form with specific reference to definitions, localisation and assessment of perineural invasion and the effects of these on incidence, outcomes, including survival and characteristics of the tumour microenvironment in primary operable colon and/or rectal cancer.

3. Results

3.1. Search results

A total of 912 potentially relevant articles were retrieved by the database search. 853 articles were excluded as they did not meet inclusion criteria (Fig. 1). Cross-referencing resulted in 4 additional articles that fulfilled the eligibility criteria. After exclusion of 25 studies as a result of incidental reporting of perineural invasion, 38 studies were reviewed.

3.2. Interpretation of results

Several factors influence recognition and interpretation of perineural invasion in colorectal cancer.

I) Currently, there is no concise, accepted definition of perineural invasion in cancer and this prevents consistent prospective reporting of perineural invasion by pathologists. According to Batsakis (1984), perineural invasion is tumour cell invasion in, around, and through nerves. Liebig et al. (2009b) has advocated a definition of perineural invasion; that include tumour cells in close proximity to neural structures (involving at least 33% of the neural circumference) or tumour cells within any of the 3 layers of the nerve sheath. In the large bowel, there are no site-specific rules for the identification of perineural invasion as two neural plexuses are located in the submucosa. One plexus lies immediately beneath the muscularis mucosa (Meissner plexus) and the deeper (Auerbach's myenteric plexus). Invasion of Auerbach's plexus is seldom recorded but may be important in terms of research. Fujita et al. (2007) defined perineural invasion as cancer cells inside the perineurium in the Auerbach plexus adjacent to the tumour front. Ueno et al. (2013) defined cancer spread along nerves of Auerbach's plexus as intramural perineural invasion and extramural perineural invasion as tumour cells invading or spreading along nerve fascicles external to the muscularis propria. Although perineural invasion has been observed intramurally and extramurally, the incidence and prognostic value based on location relative to the bowel wall have not been clarified. Perineural invasion is mostly reported as extramural (external to the muscularis pro-