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Research Article

Extracapsular Lymph Node Tumour Extension is a Potential Biomarker for Immune-modulating Therapy in Colon Cancer

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Abstract

Extracapsular lymph node tumour extension (ETE) from lymph nodes with metastatic cancer is a known negative prognostic indicator in several tumours, including colon cancer. Conversely, robust tumour-inflammatory response has been associated with favourable prognoses. We evaluated extracapsular extension of lymph node metastatic tumour in colon cancer to further study its association with clinical and histopathologic variables, and specifically, tumour-inflammatory response such as tumour-infiltrating lymphocytes and Crohn-like lymphoid reaction. We found that, compared to colon tumour cases without ETE, colon tumours with ETE occurred in younger patients, and had a higher prevalence of poorly differentiated tumours and higher tumour stage. They also had more positive lymph nodes, and more venous and perineural tumour invasion. In contrast, colon tumour cases with ETE had less Crohn-like lymphoid reaction and less tumour infiltrating lymphocytes. These findings suggest that colon tumours with ETE are inherently more biologically aggressive and are associated with less tumour-inflammatory response. Immunotherapies that bolster immune-mediated destruction of tumour cells may mitigate the negative prognostic factors associated with ETE and may be a potentially useful treatment adjunct to improve patient outcomes in this patient population.

Keywords: Extranodal Extension; Colon Cancer; Prognostic Indicators; Tumor-inflammatory Response; Tumor Infiltrating Lymphocytes; Crohn-like Lymphoid Reaction

Abbreviations

ETE: Extracapsular Lymph Node Tumour Extension

Introduction

Extracapsular tumour extension (ETE) from lymph nodes with metastatic cancer is a known negative prognostic indicator in several tumours [1], but little attention has been given to this topic [2]. In colon cancer, extracapsular tumour extension has been associated with vascular and perineural invasion and number of positive lymph nodes [3]. Conversely, tumour-infiltrating lymphocytes and lymphoid reactions have been associated with favourable prognosis [4]. We evaluated extracapsular extension of lymph node metastatic tumour in colon cancer to confirm previous findings and evaluate its association with new pathologic variables, specifically, tumour-inflammatory response. Final diagnosis summary reports from 36 clinical audit colon resections (17 with ETE and 18 without) from 2016 through 2022 were reviewed. Data on age, gender, tumour size and grade, number of positive lymph nodes, presence of venous and peri-neural invasion, Crohn-like lymphoid reaction and tumour infiltrating lymphocytes were

recorded. We found that, compared to colon tumour cases without ETE, colon tumours with ETE occurred in younger patients, and had a higher prevalence of poorly differentiated tumours and higher tumour stage. They also had more positive lymph nodes and more venous and perineural tumour invasion. Conversely, colon tumour cases with ETE had less prevalence of tumour-inflammatory response as indicated by fewer cases with Crohn-like lymphoid reaction or tumour infiltrating lymphocytes.

Materials and Methods

Following CoPath electronic archive search using keywords 'colon adenocarcinoma,' anonymized final diagnosis summary reports from 36 clinical audit colon resections (17 with ETE and 18 without) from 2016 through 2022 were reviewed. Data on age, gender, tumour size and grade, number of positive lymph nodes, presence of venous and peri-neural invasion, Crohn-like lymphoid reaction and tumour infiltrating lymphocytes were recorded. Extracapsular tumour extension refers to spread of tumour in a metastatic lymph node through the lymph node capsule into surrounding adipose tissue. Crohn-like lymphoid reaction is the presence of peritumoural lymphoid aggregates at the advancing tumour edge. Tumour-infiltrating lymphocytes refers to greater than or equal to five or more lymphocytes in contact with tumour cells. Initially colon resections and hematoxylin and eosin stained slides from paraffin embedded tissue were evaluated by consultant histopathologists and reported with College of American Pathologists synoptic tumour checklists and staged according to AJCC Cancer Staging Manual 8th edition tumour staging criteria.

Results and Discussion

Results are presented in table 1. Compared to colon tumour cases without ETE, colon tumours with ETE occurred in younger patients (mean age 68 vs. 76 years), and had a higher prevalence of poorly differentiated tumours (mean grade 3 vs. grade 2) and higher tumour stage (mean pT4 vs. pT3). They also had more positive lymph nodes (mean 11 vs. 2), and more venous (12/17; 71% vs. 4/18; 22%) and perineural tumour invasion (13/17; 77% vs. 6/18; 33%). In contrast, colon tumour cases with ETE had decreased prevalence of Crohn-like lymphoid reaction (8/17; 47% vs. 11/18; 61%) and tumour infiltrating lymphocytes (6/17; 35% vs. 8/18; 44%), compared to colon tumour cases without ETE (see Figures 1-3).

	Tumours with extracapsular extension	Tumours without extracapsular extension
Mean age (yrs)	68	76
Mean histologic tumour grade	3	2
Mean number of positive lymph nodes	11	2
Mean AJCC pathologic tumour stage	4	3
Percentage of cases with venous tumour invasion	71%	22%
Percentage of cases with peri-neural tumour invasion	77%	33%
Percentage of cases with Crohn-like lymphoid reaction to tumour	47%	61%
Percentage of cases with tumour-infiltrating lymphocytes	35%	44%

Table 1: Extracapsular tumour extension (ETE) and clinical and pathologic variables.

Figure 1: Extracapsular extension from lymph node with metastatic colonic adenocarcinoma, H and E stain, low power.

Figure 2: Tumour infiltrating lymphocytes in colonic adenocarcinoma, H and E stain, medium power.

Figure 3: Crohn-like lymphoid reaction in colonic adenocarcinoma, H and E stain, low power.

Extracapsular tumour extension (ETE) from lymph nodes with metastatic cancer is a known negative prognostic indicator in many cancers including those primary to breast, prostate and colon [1]. A more robust antitumour inflammatory response has been associated with favourable prognosis in various tumours including colon cancer [4]. We evaluated extracapsular extension of lymph node metastatic tumour in colon cancer to confirm previous findings of its association with negative prognostic indicators and to evaluate its relationship with tumour-inflammatory response, namely tumour-infiltrating lymphocytes and Crohn-like lymphoid reaction as seen in colon cancer resection specimens.

In colon cancer, extracapsular tumour extension has been associated with negative prognostic indicators including vascular and perineural invasion [3]. Extracapsular tumour extension has also been shown as an independent factor on prognosis and overall survival of colon cancer patients [5,6]. On the other hand, tumour-infiltrating lymphocytes and lymphoid reactions have been associated with favourable prognosis [4]. A deciding factor in the efficacy of treatments for metastatic cancer is the immune microenvironment and its dynamic interplay with neoplastic cells [7-9]. An important role of the immune system is to both identify and eliminate tumours. Tumour-associated antigens not found on healthy cells are recognized as "non-self" and an immune response is thereby mounted against the tumour cells. Biological response modifiers, such as interferons and interleukins, may be used to bolster the immune system by introducing larger amounts of these substances by injection or infusion with the hope of stimulating the cells of the immune system to act more effectively [10,11]. Tumour survival is promoted with upregulation by tumour cells of inflammatory inhibitors protective against tumour-associated inflammation. In lung, colorectal and head and neck cancers, immunotherapy blocking inflammatory inhibitors, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the programmed death-1 (PD-1) pathway, has been used to elicit immune-mediated destruction of tumour cells with promising results [10,11]. In ovarian cancer, tumour-infiltrating lymphocytes have been demonstrated to be associated with better prognosis, more chemosensitivity, and more cases of optimal residual tumour, and may be a potent predictive immunotherapy biomarker [12]. In colon cancer, tumour-infiltrating lymphocytes and Crohn-like lymphoid reactions have been associated with favourable prognosis [13,14].

Conclusion

We found that colon tumours with ETE occurred in younger patients and had a higher prevalence of poorly differentiated tumours with more advanced tumour stage. We confirmed previous findings that colon tumours with ETE had more positive regional lymph nodes and higher rates of vascular and perineural invasion. Colon tumours showing ETE also had less Crohn-like lymphoid reaction and less tumour infiltrating lymphocytes. Taken together, these findings suggest that colon tumours with ETE are inherently more biologically aggressive and are associated with less tumour-inflammatory response. Therefore, immunotherapies that bolster immune-mediated destruction of tumour cells may mitigate the negative prognostic factors associated with ETE, which itself may

be the result of less immune vulnerability. Immunotherapy in this patient population should be further explored as a potentially useful treatment adjunct to improve patient outcomes.

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Conflict of Interest

None.

Bibliography

1. Bhattacharya P and Mukherjee R. "Lymph node extracapsular extension as a marker of aggressive phenotype: Classification, prognosis and associated molecular biomarkers*". European Journal of Surgical Oncology* 47.4 (2021): 721-731.

2. Veronese N., *et al*. "Prognostic impact and implications of extracapsular lymph node involvement in colorectal cancer: a systematic review with meta-analysis". *Annals of Oncology* 27.1 (2016): 42-48.

3. Kim CW., *et al*. "Prognostic Implications of Extranodal Extension in Relation to Colorectal Cancer Location". *Cancer Research Treatment* 51.3 (2019): 1135-1143.

4. Väyrynen JP., *et al.* "Characteristics and significance of colorectal cancer associated lymphoid reaction". *International Journal of Cancer* 134.9 (2014): 2126-2135.

5. Li T., *et al*. "Prognostic implications of ENE and LODDS in relation to lymph node-positive colorectal cancer location". *Translation Oncology* 14.11 (2021): 101190.

6. Al Sahaf O., *et al*. "The prognostic significance of extramural deposits and extracapsular lymph node invasion in colon cancer". *Diseases of the Colon and Rectum* 54.8 (2011): 982-988.

7. Lei X., *et al.* "Immune cells within the tumor microenvironment: Biological functions and roles in cancer immunotherapy". *Cancer Letter* 1.470 (2020): 126-133.

8. Xia Y., *et al.* "Differential effects of vascular endothelial growth factor on glycocalyx of endothelial and tumor cells and potential targets for tumor metastasis". *APL Bioengineering* 6.1 (2022): 016101.

9. Apollonio B., *et al.* "Understanding the Immune-Stroma Microenvironment in B Cell Malignancies for Effective Immunotherapy". *Frontiers in Oncology* 11 (2021): 626818.

10. Kunkle C., *et al.* "The Role of the Programmed Death Receptor-1/Programmed Death Ligand-1: Immunologic Checkpoint in Human Papillomavirus–Associated Head and Neck Squamous Cell Carcinoma". *Archives of Pathology and Laboratory Medicine* 142.6 (2018): 719-720.

11. Marginean E., *et al.* "Is There a Role for Programmed Death Ligand-1 Testing and Immunotherapy in Colorectal Cancer with Microsatellite Instability? Part I—Colorectal Cancer: Microsatellite Instability, Testing, and Clinical Implications". *Archives of Pathology and Laboratory Medicine* 142.1 (2017): 17-25.

12. Santoiemma PP., *et al.* "Tumour infiltrating lymphocytes in ovarian cancer". *Cancer Biological Therapy* 16.6 (2015): 807-820.

13. Maoz A. "The Crohn's-Like Lymphoid Reaction to Colorectal Cancer-Tertiary Lymphoid Structures with Immunologic and Potentially Therapeutic Relevance in Colorectal Cancer". *Frontiers in Immunology* 22.10 (2019): 1884.

14. Page N., *et al.* "Clinical and Pathological Parameters of Tumour Infiltrating Lymphocytes in Colorectal Cancer". Atlantic Technological University, Galway, BSc Medical Science (2019).