Advances in colorectal surgery
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Citation for published version (APA):

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Chapter 13

The prognostic significance of extracapsular lymph node involvement in node positive patients with colonic cancer

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European Journal of Surgical Oncology 2008;34:390-396
Abstract

Introduction
In colonic cancer the prognostic significance of extracapsular lymph node involvement is not established and is therefore the objective of this study.

Methods
Between January 1994 and May 2005, all patients who underwent resection for primary colonic cancer with lymph node metastasis were reviewed. All resected lymph nodes were re-examined to assess extracapsular lymph node involvement. In uni- and multivariate analysis disease free survival (DFS) was correlated with various clinicopathologic factors.

Results
One hundred eleven patients were included. In 58 patients extracapsular lymph node involvement was identified. Univariate analysis revealed that pN-stage (5-year DFS pN1 vs. pN2; 65% vs. 14%, p<0.001), extracapsular lymph node involvement (5-year DFS intracapsular lymph node involvement vs. extracapsular lymph node involvement; 69% vs. 41%, p=0.003), and lymph node ratio (5-year DFS < 0.176 vs. ≥ 0.176; 67% vs. 42%, p=0.023) were significant prognostic indicators. Among these variables pN-stage (hazard ratio 3.5, 95% confidence interval [CI]: 1.72 – 7.42) and extracapsular lymph node involvement (hazard ratio 1.98, 95% CI: 1.00 – 3.91) were independent prognostic factors. Among patients without extracapsular lymph node involvement, those receiving adjuvant chemotherapy had a significantly better survival (p=0.010). In contrast, chemotherapy did not improve DFS in patients with extracapsular lymph node involvement.

Conclusion
Together with pN2 stage, extracapsular lymph node involvement reflects a particularly aggressive behaviour and has significant prognostic potential.
Introduction

The presence and extent of lymphatic dissemination are among the most important predictors for survival in colonic cancer.\(^1,2\) For stage III colonic cancer, the 5-year survival rate is approximately 50-60%.\(^3-5\) According to stages defined by the recently revised American Joint Committee on Cancer (AJCC, sixth edition) 5-year stage specific survivals were 83% for stage IIIa (T1-2N1), 64% for stage IIIb (T3-4N1), and 44% for stage IIIc (T1-4N2).\(^6\) Adjuvant chemotherapy is standard in patients with stage III disease. Adjuvant treatment with 5-fluorouracil and leucovorin reduces the risk of recurrence and death by one third.\(^4,7\)

Lymph node staging may be further refined by the identification of different levels, the absolute number of lymph nodes with metastasis, the absolute number of negative nodes, and/or the lymph node ratio (i.e. the number of involved nodes over the total number of resected and identified nodes).\(^8-10\) Furthermore, the presence of micro-metastasis in lymph nodes has also been identified as a prognostic factor.\(^11,12\)

Extracapsular lymph node involvement is the extension of cancer cells through the nodal capsule into the perinodal fatty tissue. The prognostic value of extracapsular lymph node involvement has been studied for several malignancies, including breast, oesophageal, prostate, vulva, bladder, lung, and head and neck cancer.\(^13-19\) Patients with extracapsular lymph node involvement have a reduced overall and disease free survival (DFS) in these malignancies.\(^13-20\) However, in colonic cancer the prognostic value of extracapsular lymph node involvement has not yet been established. Only one study has been published on extracapsular lymph node involvement in colonic cancer suggesting prognostic significance of extracapsular lymph node involvement.\(^21\)

Therefore, the aim of the present study was to assess the incidence and extent of extracapsular lymph node involvement in patients with node positive colonic cancer. Furthermore, its relation to other clinicopathologic factors was studied. Finally, its prognostic significance in relation to the type of recurrence was analyzed.

Methods

Patient population

Between January 1994 and May 2005, all patients who underwent segmental colonic resection in the Academic Medical Centre in Amsterdam for primary colonic cancer (rectal cancers and (sub-)total colectomies were excluded) were reviewed. All patients with lymph node involvement (stage III) were included in the present study. Patients with distant metastases (stage IV) diagnosed during preoperative staging, were excluded. Data concerning patient characteristics and performed procedure were collected during chart review using a preformatted sheet. Surgery was generally performed or supervised by a colorectal surgeon. Operations were performed with curative intent, either via median laparotomy or via laparoscopy.
Pathological processing
Routinely, after resection the pathologist who examined the operation specimen carefully palpated the specimen and all palpable lymph nodes were collected and evaluated. Routine H&E staining was performed using a standardized protocol. No additional immunohistochemical staining techniques to detect micro-metastases were used. In general all small nodes were completely embedded and serial sections were made. Larger nodes were first laminated. Subsequently they were totally embedded and serial sections were made. The findings of the pathologist were routinely discussed in a multidisciplinary meeting to evaluate the indication for adjuvant therapy. During the whole study period 5-fluorouracil based adjuvant chemotherapy was offered to all patients with lymph node involvement younger than 75 years old.

Data assessment
In the summer of 2006 an experienced pathologist re-examined all available H&E slides of both the primary tumour and all the collected lymph nodes to assess metastases and extracapsular lymph node involvement. Furthermore, pT-stage, pN-stage (i.e. ≤3 positive nodes; pN1 vs. >3 positive nodes; pN2), differentiation grade of the tumour, the presence or absence of lymphovascular invasion, total number of resected lymph nodes, total number of positive lymph nodes, lymph node ratio and the presence or absence of tumour deposits were recorded. The evaluation was done without knowledge of the clinical outcome of the patients.
Extracapsular lymph node involvement was defined as metastatic adenocarcinoma extending through the nodal capsule into the perinodal fatty tissue. Deposits of metastatic adenocarcinoma without a recognizable lymph node were not considered as extracapsular lymph node involvement but scored as separate tumour deposits and assessed as a separate pathological factor. However, the size and contour of the deposits were not taken into account in this study.
Extracapsular lymph node involvement is often associated with a desmoplastic stroma reaction. Sometimes this reaction is so extensive that the presence or absence of extracapsular lymph node involvement can be difficult to interpret. In that case, an imaginary line representing the pre-existing capsule was drawn to facilitate proper interpretation.20

Follow-up
Patients’ hospital and outpatient clinic records were reviewed to assess recurrence. To complete follow-up, a telephone survey contacting the patients’ general practitioner was done in August 2006. Follow-up extended until August 2006, ensuring a minimal potential follow-up of 15 months. Recurrence was classified as haematogenous recurrence, loco-regional recurrence (including peritoneal recurrence) or both.
Statistics
Statistical calculations were performed using SPSS® version 12.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). Age, tumour diameter, total number of resected lymph nodes (i.e. tumour positive and negative) and lymph node ratio were dichotomized as less or more than the corresponding median value. To compare categorical data the Chi-square or Fisher exact test was used when appropriate. The Mann-Whitney test was used to compare continuous variables. Survival rates were calculated on an actuarial basis with the Kaplan-Meier method, using the log-rank test for comparison. Multivariate Cox regression analysis was carried out to identify independent prognostic factors. All significant factors from a univariate analysis were entered in a multivariate analysis. P-values < 0.05 (two-sided) were considered statistically significant.

Results

Included patients
In the study period 398 patients underwent potentially curative segmental colonic resection for primary colonic cancer. In 114 patients lymph node metastases were present without other metastasis (stage III). Subsequently, three patients were excluded; two patients died due to postoperative complications, in one patient a metastasis of an earlier gastric carcinoma was diagnosed peroperatively.

In the final analysis 111 patients were included. There were 60 male and 51 female patients. Median age was 66 (range 31-91) years. Sixteen patients were operated on in an emergency setting, the remaining patients underwent elective surgery. There were 58 right sided colectomies, 15 left sided colectomies, and 38 sigmoid resections. In the included patients, a total number of 1586 lymph nodes had been identified by the pathologist who examined the resection specimen. A median of 12 (range 1-47) nodes per patient had been identified in the specimen. In one patient only a single node was identified. Metastases were detected in 332 lymph nodes. Tumour extension through the lymph node capsule was identified in a total of 101 lymph nodes and in 58 of 111 lymph node positive patients. Extracapsular lymph node involvement was confined to only one lymph node in 35 of these patients.

Clinicopathologic characteristics
The clinicopathologic characteristics of 53 patients with only intracapsular lymph node involvement and 58 patients with extracapsular lymph node involvement are summarized in Table 1. Extracapsular lymph node involvement was seen more often if the number of positive nodes was higher, in patients with pN2 disease, with a higher lymph node ratio, with poorer differentiated tumours and with invasion of lymphic or blood vessels.
Table 1. Clinicopathologic characteristics of 111 included patients with stage III colonic cancer. Patients are divided in groups with only intracapsular lymph node involvement (LNI) and patients with extracapsular LNI.

<table>
<thead>
<tr>
<th></th>
<th>Only intracapsular LNI (n = 53)</th>
<th>Extracapsular LNI (n = 58)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pT stage</strong></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>T 1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T 2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>T 3</td>
<td>50</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>T 4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour diameter (cm)</strong></td>
<td>5.0 (1.3-12.0)</td>
<td>4.9 (2.0-12.0)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Resected nodes</strong></td>
<td>11 (1-47)</td>
<td>12 (4-39)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Positive nodes</strong></td>
<td>1 (1-8)</td>
<td>3 (1-21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>pN stage</strong></td>
<td></td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>N 1</td>
<td>48</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>N 2</td>
<td>5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Lymph node ratio</strong></td>
<td>0.11 (0.02-1.0)</td>
<td>0.24 (0.08-1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Differentiation</strong></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>good</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>moderate</td>
<td>48</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>poor</td>
<td>2</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td><strong>Lymphovascular invasion</strong></td>
<td></td>
<td></td>
<td>0.031</td>
</tr>
<tr>
<td>no</td>
<td>38</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>15</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td><strong>Extranodal deposits</strong></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>no</td>
<td>40</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>13</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td><strong>Adjuvant chemotherapy</strong></td>
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<td></td>
<td>NS</td>
</tr>
<tr>
<td>no</td>
<td>17</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>35</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>unknown</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

*Values are mean (SD); †Values are median (range); ‡Fisher’s exact test, Chi-square test, Mann-Whitney U test applied when appropriate; LNI: lymph node involvement; NS: not significant

Follow-up and survival analysis

The median potential follow-up period was 74 months (range 16-151). In the follow-up period 45 patients developed recurrence; 26 patients developed haematogenous recurrence, seven patients developed loco-regional recurrence and 11 patients had both haematogenous and loco-regional recurrence. In one patient the type of recurrence was unknown. The pattern of recurrence was comparable between patients with and without extracapsular lymph node involvement (p=0.893).
Five-year DFS in patients with extracapsular lymph node involvement was 41% compared to 69% for those who had only intracapsular lymph node involvement (p=0.003, Table 2, Figure 1). No difference in DFS was observed between patients (n=35) with only one lymph node with extracapsular lymph node involvement as compared to patients (n=23) with more than one lymph node with extracapsular lymph node involvement; 5-year DFS was 41% vs. 40% (p=0.784) respectively.
Figure 1. Recurrence in patients with lymph node positive (stage III) colonic cancer. Patients are divided in groups with only intracapsular lymph node involvement (LNI) and patients with extracapsular LNI (p = 0.003).

In 30 patients tumour deposits without any recognizable lymph node structure were identified besides positive nodes. To assess whether the prognostic significance of these tumour deposits was different from extracapsular lymph node involvement, the study population was divided into three groups; intracapsular lymph node involvement and tumour deposits, extracapsular lymph node involvement without deposits and extracapsular lymph node involvement with tumour deposits. No difference in recurrence was observed between the three groups; 5-year DFS was 49%, 44% and 38% respectively (p=0.644).

Univariate analysis was performed to study the relation between the various factors and DFS. Univariate analysis revealed that pN-stage (5-year DFS pN1 vs. pN2; 65% vs. 14%, p<0.001), lymph node ratio (5-year DFS <0.176 vs. ≥ 0.176; 67% vs. 42%, p=0.023), and extracapsular lymph node involvement (5-year DFS intracapsular lymph node involvement vs. extracapsular lymph node involvement; 69% vs. 41%, p=0.003) were all significant prognostic indicators for survival (Table 2). It was shown that the presence or absence of tumour deposits was not a significant factor for recurrence in contrast to extracapsular lymph node involvement.

Multivariate analysis demonstrated that among these variables pN-stage (hazard ratio 3.5, 95% confidence interval [CI]: 1.72 – 7.42) and extracapsular lymph node involvement (hazard ratio 1.98, 95% CI: 1.00 – 3.91) were independent prognostic factors.

Adjuvant chemotherapy
Sixty-six patients received adjuvant chemotherapy, 43 patients did not, and in two patients it was unknown whether or not they had received adjuvant chemotherapy. Of the 77 patients younger than 75 years, 16 patients did not receive adjuvant chemotherapy due to
refusal by the patient or a poor performance status. Chemotherapy that was applied mostly consisted of 5-fluorouracil and leucovorin. Patients treated with adjuvant chemotherapy were significantly younger compared to those receiving no adjuvant therapy (median age was 60 vs. 77 years respectively, p<0.001). Among the other clinico-pathological factors no significant differences were observed. Overall 5-year DFS was 61% in patients who received adjuvant therapy compared to 43% in patients who did not receive adjuvant chemotherapy (p=0.067). Subsequently, the groups were divided according to the presence or absence of extracapsular lymph node involvement (Figure 2). Among the patients without extracapsular lymph node involvement those receiving adjuvant therapy had a significantly better survival compared to those who did not receive adjuvant therapy (5-year DFS was 77% vs. 48%, respectively p=0.010). In patients with extracapsular lymph node involvement the application of chemotherapy did not influence DFS; 44% vs. 39%, respectively (p=0.934).

Figure 2. Recurrence in patients with lymph node positive (stage III) colonic cancer. Patients are divided according to treatment with adjuvant chemotherapy or no adjuvant treatment and according to only intracapsular lymph node involvement (LNI) or extracapsular LNI (p=0.008).

<table>
<thead>
<tr>
<th>Numbers at risk</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracapsular LNI, no chemotherapy</td>
<td>17</td>
</tr>
<tr>
<td>Intracapsular LNI, adjuvant chemotherapy</td>
<td>35</td>
</tr>
<tr>
<td>Extracapsular LNI, no chemotherapy</td>
<td>26</td>
</tr>
<tr>
<td>Extracapsular LNI, adjuvant chemotherapy</td>
<td>31</td>
</tr>
</tbody>
</table>

Discussion

Prognostic significance of extracapsular lymph node involvement

In the present study it is demonstrated that extracapsular involvement together with pN-stage are independent prognostic parameters for recurrence (both loco-regional and haematogenous) in patients with colonic cancer.

A recent systematic review on extracapsular lymph node involvement in gastrointestinal malignancies demonstrated that the presence of extracapsular lymph node involvement is
a common phenomenon in patients with gastrointestinal malignancies. Furthermore, in all these malignancies, extracapsular lymph node involvement identified a subgroup of patients with a significantly worse long-term survival. However, for that review only one small study concerning colorectal cancer was available, including a small subgroup of patients with colonic cancer and showing that patients with extracapsular lymph node involvement had significantly worse overall- and disease-free survival as compared to patients with only intracapsular lymph node involvement. However, no multivariate analysis was performed. More recently, a larger study was published showing an incidence of extracapsular lymph node involvement of 49%. Extracapsular lymph node involvement was identified as the only independent prognosticator for recurrence in multivariate analysis (hazard ratio 3.8, 95% CI: 1.6-8.9).

The present study comprised of a consecutive series of lymph node positive patients with colonic cancer. Extracapsular lymph node involvement was associated with a higher number of positive nodes, pN2 stage, a higher lymph node ratio, poorly differentiated tumours, and invasion of lymph- or blood vessels. The prognostic significance of extracapsular lymph node involvement was confirmed in multivariate analysis demonstrating that it was an independent prognostic factor (hazard ratio 1.98, 95% CI: 1.00 – 3.91). Five-year DFS in patients with only intracapsular lymph node involvement was 69% compared to 41% in patients with extracapsular lymph node involvement (p=0.003).

In some of the included patients lymph node staging was not adequate with less than 12 sampled nodes. However, in uni- and multivariate analysis including only patients in whom 12 nodes or more were identified; the same variables were identified as significant prognostic indicators (data not shown). Another limitation of the present study is the retrospective study design. Since the resection specimen had been thrown away and only the available slide could be assessed. However, all the available slides of both the primary tumour and all the sampled nodes were re-assessed (prospectively).

The precise causative factor of the worse prognosis in patients with extracapsular lymph node involvement is not yet clear. It could be hypothesized that the ability of cancer cells to spread through the lymph node capsule, in an immunologically hostile environment, probably reflects the invasive aggressiveness of the tumour. Another hypothesis could be that extracapsular lymph node involvement reflects an extensive lymphatic spread inducing lymphatic obstruction. It has been reported that lymphatic obstruction results in an aberrant flow of lymph fluid leading to lympho-venous communication and thus to haematogenous dissemination. However, in this study there was no correlation between extracapsular lymph node involvement and recurrence pattern.

**Adjuvant chemotherapy**

In the present study no effect on survival of adjuvant chemotherapy was observed in patients with extracapsular lymph node involvement. It can be hypothesized that the extension through the barrier of the lymph node might reflect an aggressive behaviour and/or a biological insensitivity for chemotherapy. It should be taken into account that patients receiving no adjuvant therapy were significantly older, and therefore, part of this observation could be biased. However, a pooled analysis of seven randomised
trials demonstrated no significant interaction between age and the efficacy of adjuvant chemotherapy for resected colon cancer. The incidence of toxic effects was also not increased among the elderly (age > 70 years). Furthermore, about 20% of the patients younger than 75 years did not receive or refused adjuvant chemotherapy in the present study. Finally, the study concerns a retrospectively collected series of patients in a large period and the numbers in the subgroups were small introducing the risk of having a type-II-error. Therefore, there is a need for unequivocal data from large prospective studies to support this observation.

**Extranodal tumour deposits**

The proper assessment of extracapsular lymph node involvement can be difficult in the presence of extranodal deposits which are discontinuous with the primary tumour. These deposits have been identified in many gastrointestinal malignancies. It is unclear whether these are lymph nodes that have been completely replaced by tumour tissue or manifestations of multifocal metastatic disease. In the sixth edition of the TNM staging system these tumour deposits are classified as regional lymph node metastasis if the nodule has the shape and smooth contour of a lymph node. If the deposit has an irregular contour, it is classified as pT3. However, if a deposit represents a completely overgrown lymph node with extracapsular growth the contour will be irregular rather than a smooth round contour. In earlier editions of the TNM staging system all deposits larger than three millimetres in diameter were classified as regional lymph node metastasis. Tumour deposits up to three millimetres in diameter were considered as discontinuous extension and therefore classified as pT3. So the precise origin and prognostic implications of these deposits remains unclear. Therefore, in the present study these deposits were assessed as a separate factor. In the present study 27% of the patients showed these deposits. There was no correlation between the presence of these deposits and extracapsular lymph node involvement. Furthermore, these deposits had no significant effect on survival in univariate analysis. On the other hand the survival of patients with only deposits and patients with extracapsular lymph node involvement without deposits was comparable to survival of patients with both deposits and extracapsular lymph node involvement. This suggests that tumour deposits without a recognizable lymph node structure have a comparable influence on survival as extracapsular lymph node involvement.

**Conclusion**

In conclusion, two independent study groups (ours and Yano’s) indicated that extracapsular lymph node involvement in colonic cancer is an independent negative prognostic factor, reflecting a particularly aggressive biological behaviour. It identifies a subgroup of patients with a significantly worse DFS. Detection and quantification of extracapsular lymph node involvement in the surgical resection specimen might be helpful in the future to individualize postoperative therapeutic strategies in the adjuvant setting. Pathologists should be aware of this clinically important feature and report its presence and extent upon histological examination.
Reference List


