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Original Research

No change in lymph node positivity rate despite increased lymph node yield and improved survival in colon cancer

F.N. van Erning [a,*], R.M.P.H. Crolla [b], H.J.T. Rutten [c,d], L.V. Beerepoot [e], J.H.J.M. van Krieken [f], V.E.P.P. Lemmens [a,g]

[a] *Eindhoven Cancer Registry, Comprehensive Cancer Centre The Netherlands, Eindhoven, The Netherlands*
[b] *Department of Surgery, Amphia Hospital, Breda, The Netherlands*
[c] *Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands*
[d] *Department of Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands*
[e] *Department of Internal Medicine, St. Elisabeth Hospital, Tilburg, The Netherlands*
[f] *Department of Pathology, University Medical Centre St. Radboud, Nijmegen, The Netherlands*
[g] *Department of Public Health, Erasmus University Medical Centre, Rotterdam, The Netherlands*

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Abstract ***Aim:*** To analyse trends over time in the number of lymph nodes evaluated and in the proportion of node positivity and to investigate the impact on survival for patients with colon cancer.

Patients and methods: 8616 patients resected for M0 colon cancer diagnosed in the Southern Netherlands between 2000 and 2011 were included in this study. Trends in nodal evaluation and node positivity were analysed. Multivariable logistic regressions were used to assess the influence of period of diagnosis on adequate nodal evaluation ($\geqslant$12 lymph nodes) and node positivity after adjusting for patient and tumour characteristics. Crude 5-year relative survival was used as an estimate for disease-specific survival.

Results: Overall, the proportion adequate nodal evaluation increased from 13% in 2000–2002 to 59% in 2009–2011 ($p < 0.0001$), whereas the proportion node positivity remained similar across study periods (approximately 35%). Patients diagnosed in later periods were more likely to have received adequate nodal yield (adjusted Odds ratio (OR) 2009–2011 versus 2000–2002 9.8, 95% Confidence interval (CI) 8.3–11.6). However, the adjusted odds of having node positive disease did not differ between periods of diagnosis. Relative excess risk of dying was independently correlated with the number of lymph nodes evaluated (1–8 LNs versus $\geqslant$12 LNs, N0: 2.2, 95% CI 1.7–2.9; N+: 1.7, 95% CI 1.4–2.0) and period of diagnosis (2009–2011 versus 2000–2002, N+ only: 0.8, 95% CI 0.6–1.0).

* *Corresponding author at:* Eindhoven Cancer Registry, Comprehensive Cancer Centre The Netherlands, Zernikestraat 29, 5612 HZ Eindhoven, The Netherlands. Tel.: +31 40 2971616; fax: +31 40 2971610.
E-mail address: f.vanerning@iknl.nl (F.N. van Erning).

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Conclusion: The reason for improved survival with increased nodal yield is different from simple understaging as the proportion of lymph node positivity remained constant.
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1. Introduction

In the evaluation of quality of care for patients with colon cancer, the number of lymph nodes evaluated has become a surrogate marker for surgical and pathological excellence. Quality initiatives aimed at improving nodal yield have been undertaken in North America and Europe. In the Netherlands, it is measured in different auditing systems and quality registrations.

The focus on nodal yield in colon cancer was fuelled by several non-randomised studies which investigated the relationship between lymph node evaluation and survival. These studies have shown that higher lymph node yield is associated with better survival after colon cancer surgery [1–7].

Despite the attention for lymph node yield in many studies, the association with nodal positivity rate has not often been articulated. Studies from the US and Canada found that the number of lymph nodes evaluated in colon cancer has increased over the years but the proportion of metastasis containing lymph nodes did not [8,9]. Two other studies also found no association between the extent of lymph node evaluation and the proportion of lymph node positivity [10,11].

The aim of this large observational study is to evaluate trends over time in the number of lymph nodes evaluated and in the proportion of positive lymph nodes for patients who underwent resection for stage I–III colon cancer in the Southern Netherlands. More importantly, we investigated whether period of diagnosis is associated with adequate nodal evaluation and node positivity rate after adjusting for patient and tumour characteristics. Furthermore, the impact on relative survival was investigated.

2. Patients and methods

Data from the Eindhoven Cancer Registry (ECR), maintained by the Comprehensive Cancer Centre The Netherlands, were used. The ECR is a population-based registry that collects data on all newly diagnosed cancer patients in the Southern Netherlands. Information on patient and tumour characteristics, diagnosis and treatment is routinely extracted from the medical records by trained administrators. Anatomical site of the tumour is registered according to the International Classification of Disease-Oncology (ICD-O). The TNM (tumour-node-metastasis) classification is used for stage notification of the primary tumour, according to the edition valid at time of diagnosis. Comorbidities are registered according to a slightly modified version of the Charlson Comorbidity index. Socioeconomic status (SES), based on individual fiscal data on the economic value of the home and household income, is provided at an aggregated level for each postal code (covering an average of 17 households). SES was categorised as low, intermediate or high, and a separate class for postal codes of long-term care providing institutions.

2.1. Study population

All patients who underwent a radical surgical resection for primary M0 colon cancer diagnosed between 2000 and 2011 in the area of the ECR were included. Patients who underwent a local resection (i.e. polypectomy) were not included. Tumour localisation was categorised into proximal colon (comprising of caecum, appendix, ascending colon, hepatic flexure, colon transversum and splenic flexure, C18.0–C18.5), distal colon (descending colon and sigmoid, C18.6–C18.7) and colon other/not otherwise specified (C18.8–C18.9). Primary rectosigmoid and rectum tumours were excluded (C19.9 and C20.9). Patients were categorised according to their level of nodal evaluation in two ways: $\geqslant 12$ nodes examined (yes/no/unknown); and in more narrow categories (0, 1–8, 9–11, $\geqslant 12$ and unknown number >0). Adequate nodal evaluation was defined as $\geqslant 12$ nodes examined in accordance with the recommendation of the International Union Against Cancer [12]. Additionally, patients were categorised according to node positivity: N0/N+/unknown and in more narrow categories according to the number of positive lymph nodes (unknown, 0, 1–3, 4–6, $\geqslant 7$ and unknown number greater than 0). Finally, for patients with node positive disease the lymph node ratio (LNR) was calculated. The LNR is defined as the number of positive lymph nodes divided by the total number of lymph nodes evaluated. Cut-off values for the categorisation of the LNR were based on a previous study [13] in which the optimal cut-off values for prognostic differentiation were statistically calculated as 0.17, 0.41 and 0.69.

2.2. Statistical analyses

Changes in patient and tumour characteristics and lymph node yield over the study period were analysed using Chi^2 tests. Trends in node positivity across study periods for both the total study population and according to pathological T category were analysed by means of Cochran–Armitage trend tests. Multivariable logistic

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