



## Improved survival after retrieval of 12 or more regional lymph nodes in appendiceal cancer

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### Abstract

**Background:** To evaluate the role of regional lymph node (RLN) retrieval on stage migration, overall (OS), and cancer-specific survival (CSS) in appendiceal cancer.

**Methods:** Between 2004 and 2012, 1046 patients with primary stage I–III carcinoma of the appendix were identified in the Surveillance, Epidemiology and End Results database. The impact of the number of RLN removed on OS and CSS was assessed using joinpoint regression, Cox regression, and propensity score methods.

**Results:** The rate of node-positive cancer increased with the number of retrieved RLN from 10.5% in patients with one RLN removed to 30.6% in patients with 10 RLNs removed. This leveling off at 10 RLN was confirmed by joinpoint regression analysis ( $p = 0.023$ ). Despite the finding that retrieval of 10 RLN should be sufficient for appendiceal cancer, for the survival analysis the somewhat higher cutoff of 12 RLN was applied, since this cutoff is recommended by the guidelines for colorectal cancer. Retrieval of 12 or more RLN was beneficial compared to less than 12 RLN retrieved for OS (HR = 0.60,  $p < 0.001$ ) and CSS (HR = 0.67,  $p = 0.020$ ) in multivariable analysis, as well as in propensity score matched analysis (OS: HR = 0.58,  $p = 0.001$ , CSS: HR = 0.61,  $p = 0.005$ ).

**Conclusion:** The rate of node-positive cancer increased with the number of retrieved RLN up to about 10 RLN (95%CI: 3.6–16.3,  $p = 0.023$ ). Over 10 retrieved RLN, the node-positive cancer rate no longer increased. This correlates with the recommended number of 12 RLN to be retrieved in colorectal cancer, but differs from the guideline for neuroendocrine tumors.

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**Keywords:** Appendiceal cancer; Lymph nodes; Survival

### Introduction

Malignancies of the appendix are scarce. Most of them are incidentally detected during appendectomy. The majority of the tumors are carcinoids, adenomas or lymphomas. In about one out of 100 appendectomies, adenocarcinomas are found, and their optimal treatment remains controversial.<sup>1</sup>

According to a report by the National Cancer Institute, appendiceal neoplasms account for roughly 0.4% of

gastrointestinal tumors,<sup>2</sup> and can present with various histologies. With 66%, carcinoids are by far the most common type, followed by cyst-adenocarcinoma with the incidence of 20% and adenocarcinoma with 10%.<sup>1</sup> Rare entities include adenocarcinoid, signet ring, non-Hodgkin's lymphoma, ganglioneuroma, and pheochromocytoma.<sup>3</sup>

Most primary cancers of the appendix are diagnosed at an age between 55 and 65, with exception of malignant carcinoids with a mean age at diagnosis of 38 years. Risk for all appendiceal neoplasms does not seem to differ between genders, except for malignant carcinoids affecting three times more women than men.<sup>2</sup>

Opposite to the removal of RLN in colorectal cancer, there is no consensus on the optimal number of resected

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RLN in patients with appendiceal adenocarcinoma. The consensus standard for hospital-based performance of colon cancer resections recommends the removal of at least 12 RLN.<sup>4</sup> With increasing numbers of RLN removed, quality of cancer staging improves and survival is prolonged.<sup>5,6</sup> Some authors suggest to remove more than 12 RLN to achieve a more accurate staging regarding the number of positive RLN and consequentially to performed a better suited therapy.<sup>7</sup>

This population-based analysis aimed to identify by trend analysis and joinpoint regression the optimal number of retrieved RLN for an optimal staging, and to compare it to the 12 RLN recommended for colorectal cancer resection. To assess the effect of lymph node removal on survival, a propensity score matched Cox regression minimizing the bias by potential confounders was performed.

## Methods

### *Cohort definition: surveillance, epidemiology and end results*

Data from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute in the United States were the source of this population-based analysis. SEER data were collected and reported using data items and codes as documented by the North American Association of Central Cancer Registries (NAACCR).<sup>8</sup> Primary cancer site and histology were coded according to criteria found in the third edition of the International Classification of Diseases for Oncology (ICD-O-3).<sup>9</sup> Patients with carcinoma of the appendix were identified by the ICD-O-3 site code C181 and the behavior code 3 (NAACCR items 522 and 523). Patients diagnosed at autopsy or by death certificate, as well as patients with no histologically confirmed cancer, were excluded (NAACCR items 490 and 2180). Patients with histological types other than adenocarcinoma (NAACCR item 522), patients with a lifetime occurrence of another primary malignancy (NAACCR item 380), patients without the oncological resection of the cancer (NAACCR items 1290), patients who preoperatively received radiation (NAACCR item 1360), and patients without retrieved regional lymph nodes (NAACCR item 830) were excluded (Fig. 1).

### *Statistical analyses*

Statistical analyses were performed using the R statistical software ([www.r-project.org](http://www.r-project.org)). A two-sided p-value <0.05 was considered statistically significant. Continuous data are expressed as the mean  $\pm$  standard deviation. Chi-square tests were used to compare proportions. In the regression analysis, all p-values were computed by likelihood ratio tests. Wald-type confidence intervals were estimated.

To test for a significant correlation between the number of retrieved RLN and the rate of node-positive carcinomas, Spearman's rho was applied. The rate of node-positive carcinomas was modeled by logistic regression, and Davies-tests<sup>10</sup> were applied to test for breakpoints in the number of RLN at which a significant change in the rate of node-positive carcinomas had occurred. Joinpoint regression analysis was applied to define the best fitting points for changes in the trend of the rate of node-positive carcinomas.<sup>11</sup> For sensitivity analysis, the relationship between the number of RLN and the rate of node-positive carcinomas was finally assessed utilizing loess regression analysis.<sup>12</sup>

Patients with retrieval of 1–11 and 12 or more RLN were compared, the factorized number of retrieved RLN was assessed as a prognostic factor for overall and cancer-specific survival utilizing a Kaplan–Meier and Cox regression analysis with and without risk-adjustment for stage, histology, grading, year of diagnosis, age, gender, ethnicity, and marital status (risk set). The proportional hazard assumption was tested utilizing scaled Schoenfeld residuals and by the inspection of hazard ratio (HR) plots.<sup>13</sup> Predictors of the number of retrieved RLN in the risk set were assessed with multivariable logistic regression. Propensity score analysis to adjust for potential baseline confounding variables was performed.<sup>14–16</sup> The “MatchIt” and the “optmatch” R packages were used to perform a bipartite weighting propensity score analysis.<sup>17,18</sup> The distance measure was estimated by logistic regression using the risk set described above. Patients with 1–11 retrieved RLN who did not have a counterpart regarding the distance measure among the patients with 12 or more retrieved RLN and vice versa were excluded. Afterward, the baseline risk profiles of the matched patients were compared to assure that no major differences in baseline patient characteristics existed. The prognostic value of 1–11 versus 12 or more retrieved RLN for overall and cancer-specific survival was assessed with a Cox regression analysis applying the weights and strata obtained by the bipartite matching propensity score analysis.

## Results

### *Patient characteristics*

For the time period 2004–2012, 1046 patients with appendiceal cancer were selected from the SEER database (Fig. 1). The mean follow-up was  $40.9 \pm 29.2$  months. At the end of the follow-up, 829 (79.2%) patients were alive, 167 (16%) patients had died of appendiceal cancer and 50 (4.8%) patients deceased due to other reasons. The mean number of resected RLN was  $16.9 \pm 10$ .

### *Trend analysis of lymph node retrieval and N-stage*

The rate of node-positive cancer increased with the number of retrieved RLN. The rate of node-positive appendiceal

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