

## Prognostic Significance of Lymph Node Metastases in Patients with High-Grade Appendiceal Cancer

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### ABSTRACT

**Background.** In treating high-grade appendiceal cancer, appropriate patient selection for cytoreductive surgery and heated intraperitoneal chemotherapy (CRS/HIPEC) is essential. The effect of lymph node (LN) status on survival is not clear. We hypothesize that LN metastases negatively affect long-term survival.

**Methods.** Retrospective analysis of peritoneal mucinous carcinomatosis (PMCA) patients from a prospective database was conducted. Using Kaplan-Meier survival curves and Cox proportional hazards ratio analysis, the effect of LN status, completeness of cytoreduction (CC), and peritoneal cancer index (PCI) was studied.

**Results.** Of 134 patients with appendiceal cancer who underwent CRS/HIPEC, 77 (57%) had PMCA. Mean follow-up was 22 (range, 3–90) months. Overall survival (OS) was 88, 56, and 40% for 1, 3, and 5-year, respectively. Thirty-four patients (44%) had LN metastases, 23 of whom (68%) had CC, whereas in LN negative patients 35 of 43 (81%) had CC ( $p = 0.191$ ).  $PCI \geq 20$  was seen in 23 of 34 patients (68%) with LN metastases and 29 of 43 (67%) without metastases ( $p = 0.191$ ). Five-year OS for patients with LN metastases was 11% compared with 76% for LN negative ( $p < 0.001$ ). Among patients with complete cytoreduction, 5-year OS for LN positive vs. negative was 21 and 73%, respectively ( $p = 0.002$ ). On multivariate regression analysis of LN status, CC score and PCI, the following hazard ratios were obtained: 3.4 (95% confidence interval (CI), 1.3–9.0), 2.6 (95% CI, 1.03–6.7), and 2.8 (95% CI, 0.8–10.4), respectively.

**Conclusions.** Patient selection for CRS/HIPEC should take into consideration LN status, but it should not be a contraindication if preoperative evaluation revealed a high likelihood of complete cytoreduction.

Epithelial appendiceal cancer is a rare but devastating disease that presents usually after peritoneal spread.<sup>1</sup> Peritoneal metastases can range from a few benign-appearing cells dispersed in mucin to very aggressive-appearing histopathology, including signet ring cells. Tumor grade at presentation is an important prognostic variable.<sup>2,3</sup> The low-grade variant has no potential for lymph node (LN) metastasis. On the other hand, high-grade tumors have the histological characteristics that will allow lymphatic and hematogenous spread in addition to their peritoneal seeding.

Cytoreduction and heated intraperitoneal chemotherapy (CRS/HIPEC) has been shown to be an effective treatment for carcinomatosis from appendiceal cancer.<sup>1,4–7</sup> However, patient selection criteria for such an aggressive treatment approach are not well established. In the recent edition of the American Joint Commission Cancer Staging Manual, appendiceal cancers are staged separate from their colorectal counterpart, with LN status as an integral part of this classification system.<sup>8</sup> The incidence of LN metastases in appendiceal cancer has been reported to range from 4 to 30%.<sup>9</sup> The prognostic significance of regional LN status on survival has not been well reported in appendiceal cancer, most likely due to the rarity of the disease and because historically these tumors have been classified with colorectal cancers.

In a study by Gonzalez-Moreno et al., LN metastases were shown not to affect survival after CRS/HIPEC in patients with appendiceal cancer.<sup>9</sup> In a more recent publication, the same group reported minimal significance of LN metastases on overall survival.<sup>10</sup> This study analyzed the prognostic value of LN metastases in patients with peritoneal seeding from high-grade appendiceal cancer who

underwent CRS/HIPEC. We hypothesize that LN metastases adversely affect prognosis in these patients.

## METHODS

Patients with appendiceal cancer and peritoneal spread who underwent CRS/HIPEC during the years 1999–2010 were identified from a prospective database. All patients participated in an institutional review board-approved protocol, and preoperative informed consent was obtained. High-grade disease was defined as peritoneal mucinous carcinomatosis (PMCA) per Ronnett's classification.<sup>2,3</sup> CT scans of the chest, abdomen, and pelvis, and tumor markers (CEA, CA19-9, and CA 125) were obtained before surgery. After a review of the CT scans and the patient's functional status (ECOG 0, 1), surgery was recommended if complete cytoreduction was deemed feasible. Prior surgery score (PSS) was assessed as previously described by Jacquet and Sugarbaker.<sup>11</sup> A single surgeon performed all operations. Of the 134 patients with appendiceal cancer and peritoneal spread, 77 patients with PMCA who underwent their first CRS/HIPEC at our institution were included.

Most patients had an initial surgery at another institution before their CRS/HIPEC. Patients were divided into two groups based on the presence or absence of LN metastases. The numbers of harvested and positive LN nodes were calculated by adding numbers reported from CRS to those reported in the prior surgery.

Under general anesthesia, a xypho-pubic incision was made. Disease extent was assessed at the beginning and after CRS, by calculating peritoneal cancer index (PCI) score as previously described by Jacquet and Sugarbaker.<sup>11</sup> Resections were done as needed to achieve complete cytoreduction, including but not limited to excision of previous scar and port sites, anterior abdominal wall peritonectomy, splenectomy, cholecystectomy, greater and lesser omentectomy, diaphragmatic and pelvic peritonectomies, stripping of peritoneum over omental bursa and porta hepaticus, and visceral peritonectomies. To preserve postsurgical quality of life, bowel and solid organs were removed only if they were extensively involved or could not be cleared by using other methods. Every attempt was made to avoid stomas and extensive small-bowel resections.

After CRS, HIPEC was performed by using a closed technique for 90 minutes (before performing any anastomoses). Complete cytoreduction (CC) was defined as no visible tumor nodules or nodules < 2.5 mm in size, using the CC score adopted by the consensus panel recommendations on peritoneal surface malignancies.<sup>12</sup> Mitomycin-C was used with a dose of 40 mg: 30 mg given at time zero and 10 mg given 30 minutes later. The target outflow temperature was maintained at 41–42°C. Urine output was

maintained between (250–400 cc/h) during perfusion to avoid renal toxicity.

Patients were transferred to the intensive care unit during the first 24 hours of the postoperative period and then to the surgical floor when stable. Early mobilization was encouraged. Physical therapy assisted with ambulation beginning on postoperative day 1. Low molecular weight heparin, compression stockings, and early mobilization were used for deep vein thrombosis prophylaxis. Patients were discharged when clinically stable; low molecular weight heparin was continued for 21 days.

Follow-up was performed at 3 weeks, 3 months, and every 6 months thereafter. CEA, CA19-9, and CA 125 with CT scans of the chest, abdomen, and pelvis were performed 1-month postoperatively, at 6-month intervals for 5 years, and yearly thereafter. No patients were lost to follow-up.

Data were collected prospectively at patients' follow-up visits. Comparisons between groups were performed by using the chi-square test for categorical variables and the analysis of variance for continuous variables. Overall survival (OS) was calculated from the date of CRS/HIPEC to the date of death. Estimates of survival were calculated by using the Kaplan-Meier method. Differences were calculated with a log-rank test. Pertinent variables were compared using the Cox proportional hazard ratio. Multivariate regression analysis was performed using Cox proportion hazard regression model. Results were considered statistically significant if  $p < 0.05$ . The institutional review board approved this study.

## RESULTS

Seventy-seven patients with PMCA were entered into the study. The female to male ratio was 44/33. The mean age at diagnosis was 50 (range, 26–74) years. The mean age at surgery was 52 (range, 27–79) years (Table 1).

Fifty-two patients had PCI score  $\geq 20$  (68%) and 53 had PSS of 2 or 3 (69%). Complete cytoreduction was achieved

**TABLE 1** Patients' demographics and characteristics

	LN-negative	LN-positive	<i>p</i>
Male	16	17	0.26
Female	27	17	0.26
Mean age at diagnosis (year)	51	50	0.543
Mean age at surgery (year)	53	51	0.527
Mean age at last F/U (year)	55	53	0.457
CC	35 (81%)	23 (68%)	0.191
PCI $\geq 20$	29 (67%)	23 (68%)	0.191
PSS 2 or 3	29 (67%)	24 (73%)	0.802

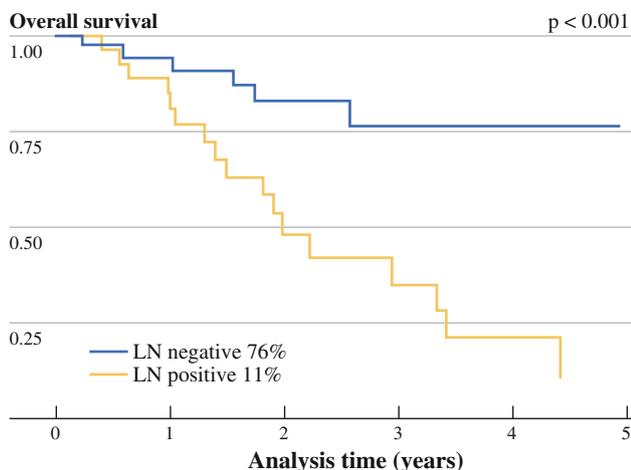
LN lymph node, F/U follow-up, CC complete cytoreduction, PCI peritoneal cancer index, PSS prior surgery score

in 58 patients (75%). Thirty-four had LN metastases (44%). The mean number of positive LN was 8 (range, 1–49). The mean number of harvested LN was 19 (range, 1–84). For patients with LN metastases, 23 of 34 (68%) had CC, whereas for LN-negative patients, 23 of 43 (81%) had CC ( $p = 0.191$ ). For patients with LN metastases, 23 of 34 (68%) had  $PCI \geq 20$ , whereas in LN-negative patients, 29 of 43 (67%) had  $PCI \geq 20$  ( $p = 0.191$ ). For patients with LN metastases, 24 of 34 (73%) had PSS of 2 and 3, whereas in negative patients, 29 of 43 (67%) had PSS of 2 or 3 ( $p = 0.802$ ; Table 1).

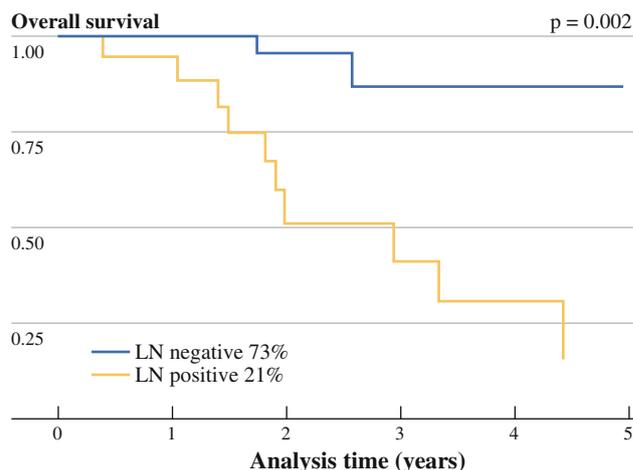
At a mean follow-up of 22 (range, 3–90) months, 53 of 77 patients (69%) were alive, 37 of whom (48%) exhibited no evidence of disease. Thirty-one of those were LN-negative and 6 were LN-positive ( $p < 0.001$ ), whereas 16 (21%) were alive with disease. Twenty-four patients were dead: 22 of 77 (29%) from disease and 2 from other causes. Seventeen of these patients had LN metastases, and five did not ( $p < 0.001$ ).

Calculated OS for all PMCA patients was 88, 56, and 40% for 1, 3, and 5 years, respectively. The median survival was 3.4 years. The 5-year OS was 52% for patients with CC and 0% for patients with incomplete cytoreduction ( $p < 0.001$ ). The 5-year OS was 66% for patients with  $PCI < 20$  and 29% for patients with  $PCI \geq 20$  ( $p < 0.015$ ). The 5-year OS was 48% for patients with PSS of 0 or 1, similar to the 52% OS in patients with PSS of 2 or 3 ( $p = 0.895$ ).

The 5-year OS was 76% for LN-negative status and 11% for LN-positive patients ( $p < 0.001$ ; Fig. 1). Among patients with complete cytoreduction, the 5-year OS for LN negative vs. positive patients was 73 and 21%, respectively ( $p = 0.002$ ; Fig. 2). On multivariate regression analyses, including LN status, CC score, and PCI, the following hazard ratios and confidence intervals were



**FIG. 1** Overall survival by lymph node status in years



**FIG. 2** Overall survival with complete cytoreduction by lymph node status in years

obtained: 3.4 (95% CI, 1.3–9.0), 2.6 (95% CI, 1.03–6.7), and 2.8 (95% CI, 0.8–10.4), respectively.

Thirty-day postoperative and in-hospital mortality was zero. Major postoperative complications included pancreatic leak in eight patients (10.4%), anastomotic leak that developed a fistula in one patient (1.3%), pneumonia in ten patients (13%), and acute renal failure in two patients (2.6%).

## DISCUSSION

Complete cytoreduction (CC), PCI score, and histology are important predictors of overall survival in appendiceal cancer with peritoneal spread.<sup>7,10</sup> LN metastasis has not been shown in previous studies to affect survival.<sup>9,13</sup> This study evaluated LN status in patients with PMCA only, because patients with disseminated peritoneal adenomucinosis (DPAM) rarely have LN metastases, and if found, it was suspected to be an error in the diagnosis. The rate of LN metastases in PMCA was 44%, which is higher than what has been previously reported.<sup>9</sup> This may be due to a combination of evaluating only PMCA tumors and thorough harvesting of LN in this series. LN status emerged as a statistically significant variable that affected overall survival, even when adjusted for CC and PCI score. Multivariate regression analysis revealed an adverse hazard ratio of 3.4 for LN metastasis (95% CI, 1.3–9.0).

Gonzalez-Moreno et al. reported a 5% rate of LN metastases in appendiceal cancer.<sup>9</sup> Of 25 patients with LN metastases, 16 (64%) had PMCA and 4 had DPAM. On the other hand, of the 95 patients who had no LN metastases, 30 (32%) had PMCA and 40 had DPAM. The difference in histology between LN-positive and LN-negative groups was statistically significant in their study; the groups also included patients with hybrid pathology. They concluded that LN status did not affect survival. However, it is generally accepted that

patients with DPAM have better outcome than PMCA patients.<sup>2,3,7,10</sup> It would seem that comparing these two groups reflects factors other than just LN status. In our study population, when adjusted for other pertinent variables, LN status was a statistically significant prognostic factor and predictor of survival. Because of the complexity and possible complications of CRS/HIPEC, selecting patients who will benefit the most from the procedure is essential. The results of our study suggest that LN status should be considered when evaluating these patients for treatment.

Our study has several limitations, including retrospective nature, underlying selection bias, and the combined LN status reported from a patient's first surgery and CRS/HIPEC. Because first surgeries varied from a biopsy to major debulking, LN status was not always available. Another important question that remains to be answered is which LN basins should be removed other than the ileocolic. The omentum and peritoneum are frequently involved and omentectomy/peritonectomy is a standard part of CRS/HIPEC. Eighteen of 34 patients in this study had metastatic nonregional LN, mainly found in the rectosigmoid specimen. None of those 18 patients was alive at 5 years. The extent of LN dissection at CRS/HIPEC and standardization of pathological evaluation of the cytoreduction specimen need to be addressed through collaboration of experienced surgeons and pathologists in that field and implementation of multi-institutional clinical trials.

Currently, we recommend adjuvant chemotherapy to all patients with PMCA after CRS/HIPEC. However, reports about the efficacy of systemic chemotherapy for appendix cancer are scarce.<sup>14,15</sup> Delaying CRS/HIPEC will lead to disease progression and lower the chances of CC, which has been shown to be essential for long-term survival.<sup>4,5,7</sup> On the other hand, from our experience, systemic chemotherapy is delayed after CRS/HIPEC due to the morbidity of the procedure. Therefore, the question will arise about the effectiveness of short duration precytoreduction chemotherapy for patients with PMCA and LN involvement. Due to the complexity in decision making, these patients are better managed through a multidisciplinary approach preferably by a team with expertise in peritoneal surface malignancy. In addition, with such a rare disease, a multi-institutional, randomized, clinical trial is essential to answer the above-mentioned questions.

In conclusion, this study revealed the prognostic significance of LN status. However, the number of LN to be harvested in appendiceal cancer has not been standardized. Multi-institutional efforts should be made to classify further patients with positive LN into subcategories based on the ratio or number of positive LN. We recommend radical right hemicolectomy and thorough LN sampling in patients with PMCA. Patient selection for CRS/HIPEC should take into consideration LN status from previous surgeries; however, the presence of LN metastases should not be a

contraindication to CRS/HIPEC if preoperative evaluation indicates a strong possibility for CC, because a 21% 5-year OS could be achieved in this high-risk group.

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