

# Increased number of metastatic lymph nodes in adenocarcinoma of the ampulla of Vater as a prognostic factor: A proposal of new nodal classification

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**Background.** Although the number of metastatic lymph nodes in most gastrointestinal carcinomas is correlated inversely with prognosis, the prognostic value of the number of metastatic lymph nodes in ampullary adenocarcinoma has not been well characterized.

**Methods.** Lymph node metastasis was assessed in the Surveillance, Epidemiology and End Results database in 1,057 ampullary adenocarcinomas that were operatively resected and for which at least 12 lymph nodes were examined. A complex pattern of survival versus extent of lymph node metastasis was captured by censored local regression. The impact of the extent of lymph nodes metastasis on survival was investigated by use of the K-adaptive partitioning algorithm to identify the most significant cut-off points of metastatic lymph nodes affecting survival.

**Results.** Two significant cut-off points (0 and 2) for the metastatic lymph node segregated patients into 3 groups with clinically important differences in median survival: patients with no metastatic lymph node (477 cases) had a median survival of 91 months, patients with 1-2 metastatic lymph nodes (279 cases) had a median survival of 29 months, whereas patients with  $\geq 3$  metastatic lymph nodes (301 cases) had a median survival of 19 months ( $P < .0001$ ). These results were validated with additional single institution dataset (318 cases,  $P < .0001$ ).

**Conclusion.** The present results suggest that the nodal classification of ampullary adenocarcinoma should be categorized N0 (no metastatic lymph node), N1 (1-2 metastatic lymph nodes), and N2 ( $\geq 3$  metastatic lymph nodes). (Surgery 2014;155:74-84.)

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ADENOCARCINOMAS of the ampulla of Vater are relatively rare malignant neoplasms, representing only 0.5% of all gastrointestinal malignancies.<sup>1</sup> The

incidence rate of ampullary adenocarcinoma has been increasing since 1973 to reach 0.9 per 100,000 persons in the United States.<sup>1</sup> Ampullary adenocarcinomas tend to be detected relatively in the early stage, have a greater resectable rate at the time of diagnosis than other periampullary cancers,<sup>2,3</sup> and have a more favorable prognosis than adenocarcinomas from the pancreas or common bile duct.<sup>4-6</sup>

Several prognostic factors, including histologic grade, pancreatic invasion, lymphatic invasion, perineural invasion, resection marginal status, and lymph node metastasis, affect the survival of patients with ampullary adenocarcinoma after operative resection.<sup>7-11</sup> The presence of lymph node metastasis is one of the most important prognostic factors in the disease.<sup>7-11</sup> The number of metastatic lymph nodes is an important prognostic factor in many carcinomas, including carcinomas of the esophagus, esophago-gastric junction,

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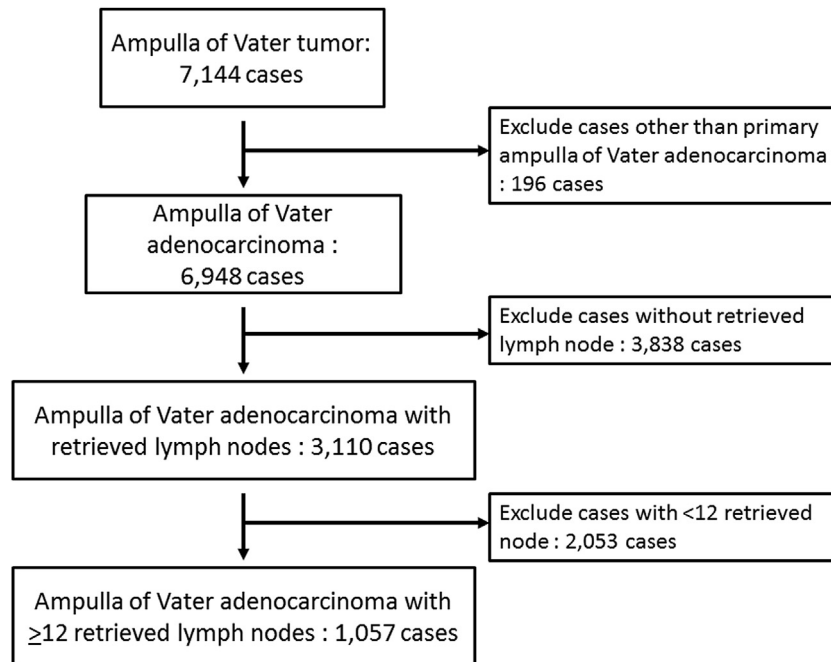
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**Fig 1.** Flow diagram showing exclusion criteria for the selection of ampullary adenocarcinoma patients from the SEER database.

stomach, small intestine, appendix, colon, rectum, bladder, ovary, and breast.<sup>12</sup> For those carcinomas, the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) cancer staging manual has adopted the number of metastatic lymph nodes as nodal (N) classification<sup>12</sup>; for ampullary adenocarcinoma, however, the manual just categorized regional lymph nodes as absent (N0, no regional lymph node metastasis) or present (N1, regional lymph node metastasis). Several studies recently reported that the number of positive lymph nodes is an independent prognostic factor in ampullary adenocarcinoma<sup>7,12-14</sup>; the small number of cases tested and the reliance on single institutions, however, limits the general applicability of their results.

Therefore, in the present study we investigated the effect of the number of metastatic lymph nodes on the survival of ampullary adenocarcinoma patients by using the Surveillance, Epidemiology, and End Results (SEER) population database and subclassified nodal status using the *K*-adaptive partitioning statistical (KAPS) algorithm. In addition, a validation study was performed to demonstrate the accuracy of proposed N classification of ampullary adenocarcinoma with single institution cases.

## MATERIALS AND METHODS

**Case selection.** A total of 7,144 patients with ampulla of Vater tumors were selected from 490,081 cases of gastrointestinal tract tumors other than

colorectal tumors from the SEER database. The 2008 November submission data of the SEER9 registry from the SEER website (<http://seer.cancer.gov>) was used for the present study. The SEER9 registry compiled data from 1973 to 2008 and covers approximately 9.5% of the U.S. population, including San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta. One hundred ninety-six cases with nonadenocarcinomas, including neuroendocrine tumors, were excluded from the 7,144 cases of ampullary tumors (Fig 1). From the remaining 6,948 patients with ampullary adenocarcinoma, 3,838 patients for whom no information was available regarding lymph node assessment were excluded. Therefore, complete nodal staging data were available for 3,110 cases of ampullary adenocarcinoma. During the analysis, 1,057 cases of surgically resected ampullary adenocarcinoma for which at least 12 lymph nodes had been examined were selected, since the retrieval of a minimum of 12 lymph nodes is recommended in the 7<sup>th</sup> edition of the AJCC cancer staging manual for accurate staging.<sup>12</sup> In addition, 2,051 ampullary adenocarcinoma cases with fewer than 12 lymph nodes examined also were evaluated during the validation phase of the study.

**Data collection.** The clinicopathologic variables investigated in the test set from SEER database included sex, age, tumor size, T classification, M classification, total number of lymph nodes

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