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# Is Para-aortic Lymph Node Metastasis a Contraindication for Radical Resection in Biliary Carcinoma?

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**Abstract**
*Background* Para-aortic nodal dissection in patients with biliary carcinoma has not been performed routinely worldwide. Therefore, the prognostic impact of para-aortic lymph node metastasis in biliary carcinoma has not yet been evaluated. The aim of this study was to clarify the prognostic impact of para-aortic lymph node metastasis in biliary carcinoma.
*Methods* Of 113 patients with biliary adenocarcinoma who underwent surgical resection with regional and para-aortic lymph node dissection, para-aortic lymph node metastasis was found in 17 patients (15%) by final pathological examination. Relationships between clinicopathological factors, including para-aortic lymph node metastasis, and survival were analyzed by univariate and multivariate analyses.
*Results* Overall survival rates for the 113 patients were 82% at 1 year, 65% at 2 years, 58% at 3 years, and 52% at 5 years. Univariate analysis revealed that better tumor differentiation ($P = 0.044$), negative lymph node metastasis ($P < 0.001$), negative para-aortic lymph node metastasis ($P = 0.007$), negative surgical margin status ($P < 0.001$), lower UICC pT factor ($P = 0.009$), and earlier UICC stage ($P < 0.001$) were associated significantly with longer survival. Lymph node metastasis ($P = 0.004$) but not para-aortic lymph node metastasis ($P = 0.323$) remained associated independently with longer survival by multivariate analysis. Five-year survival rates for node-negative patients, node-positive patients without para-aortic lymph node metastasis, and node-positive patients with para-aortic lymph node metastasis were 72, 31, and 24%, respectively.
*Conclusion* Radical resection should not be abandoned for patients with para-aortic lymph node metastasis in biliary adenocarcinoma.

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## Introduction

The prognosis of biliary carcinoma remains dismal because in most patients with this disease the diagnosis is made at an advanced stage despite advances in diagnostic modalities. In order to improve long-term outcome of patients with biliary carcinoma, several surgeons have advocated aggressive surgical resection, including major hepatectomy [1, 2], pancreatoduodenectomy [3, 4], extended lymphadenectomy [5, 6], and vascular resection [7, 8], because complete surgical resection provides the only curative treatment option in this disease. These cited surgical series have demonstrated useful prognostic factors, including tumor differentiation [2], surgical margin status [2, 3, 6], and use of adjuvant therapy [5]. In addition, lymph node status is reported to be one of the most important prognostic factors for patients with resected biliary carcinoma, including intrahepatic cholangiocarcinoma [9, 10], hilar cholangiocarcinoma [6], distal cholangiocarcinoma [3–5], carcinoma of the gallbladder [11, 12], and ampullary carcinoma [13, 14]. According to previous reports concerning lymphatic spreading pattern of biliary carcinoma, biliary carcinoma initially spreads to the nodes in the hepatoduodenal ligament, and finally to the para-aortic lymph nodes through the retropancreatic nodes or the nodes around the common hepatic artery [15–18]. Several investigators have

recommended dissection of these lymph nodes for curative resection of biliary carcinoma [15–17]. However, there have been few reports concerning the significance of para-aortic lymph node metastasis, and prognostic impact of para-aortic lymph node metastasis in biliary carcinoma has not yet been evaluated [11, 19–23].

In our institution, dissection of para-aortic lymph nodes as well as the regional lymph nodes in patients with biliary carcinoma has been performed routinely for recent years. The aim of this study was to clarify the prognostic impact of para-aortic lymph node metastasis in biliary carcinoma by assessing cases treated at a single institution with univariate and multivariate survival analyses.

## Patients and methods

### Study design

Two hundred forty-eight patients with biliary adenocarcinoma (22 with intrahepatic cholangiocarcinoma, 55 with hilar cholangiocarcinoma, 56 with distal cholangiocarcinoma, 56 with carcinoma of the gallbladder, and 59 with ampullary carcinoma) underwent surgical resection with curative intent at the Department of Surgery, Hiroshima University Hospital, between January 1992 and December 2009. All 248 patients underwent regional lymph node dissection. Moreover, patients who underwent surgical resection before 2006 underwent para-aortic lymph node dissection at the discretion of the surgeon, and dissection of para-aortic lymph node was routinely performed for patients who underwent surgical resection after 2007. As a result, 113 patients underwent surgical resection with regional and para-aortic lymph node dissection; none had para-aortic lymph node metastasis based on preoperative imaging examinations. All patients underwent R0 or R1 tumor resection and had confirmed pathological diagnosis of adenocarcinoma arising from the biliary tract. Pathological variants, including neuroendocrine tumor and combined hepatocellular and cholangiocellular carcinoma, were excluded from analysis. Relationships between clinicopathological factors, including para-aortic lymph node metastasis, and survival were analyzed by univariate and multivariate analyses. Written informed consent was obtained from all patients for surgical treatment and pathological examinations according to the institutional guidelines.

### Preoperative workup and surgical procedure

Preoperative workup included ultrasonography, computed tomography, endoscopic sonography, endoscopic retrograde pancreatocholangiography, and percutaneous transhepatic cholangiography to evaluate the local or distant extension of the tumors. Tumor resection was abandoned if distant metastasis, invasion to the celiac or superior mesenteric artery, and apparent para-aortic lymph node metastasis were found by these preoperative examinations. If jaundice was identified preoperatively, endoscopic retrograde biliary drainage or percutaneous transhepatic biliary drainage was performed to reduce the cholestatic liver damage. In addition, preoperative percutaneous transhepatic portal embolization for the liver segment to be resected was utilized to induce compensatory hypertrophy of the future remnant liver if the estimated resected liver volume, which was calculated by computed tomography, exceeded 60% of the whole liver.

Patients with distal cholangiocarcinoma and ampullary carcinoma typically underwent pancreatoduodenectomy with or without pylorus preservation, while surgical procedures for patients with intrahepatic cholangiocarcinoma, hilar cholangiocarcinoma, and carcinoma of the gallbladder almost always included a wide variety of hepatectomy. All patients underwent regional and para-aortic lymph node dissection. The para-aortic lymph nodes were dissected from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery. Intraoperative pathological assessment of the proximal or distal ductal margins was performed using frozen tissue sections. If the ductal margin was positive for cancerous cells, further resection of the pancreas was performed to the maximum extent possible.

### Pathological investigation

After tumor resection, all specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Pancreatic invasion, duodenal invasion, hepatic invasion, and lymph node metastasis were all determined pathologically. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the proximal hepatic transection line, distal bile duct transection line, or dissected periductal soft tissue margins. The final stage of biliary carcinoma was examined pathologically according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 7th edition [24].

### Postoperative adjuvant chemotherapy

Adjuvant chemotherapy was administered at our institution beginning in 2002. Eligibility criteria for gemcitabine-based adjuvant chemotherapy included an Eastern Cooperative Oncology Group performance status of 0–1,

adequate bone marrow reserve (white blood cell count >3000/mm$^3$, platelet count >100,000/mm$^3$, hemoglobin level >8 g/dl), and adequate renal (serum creatinine concentration <1.5 mg/dl) and liver function (total serum bilirubin concentration <3 mg/dl).Patients who were offered chemotherapy postoperatively had two options based on disease stage, as previously described [25, 26]. Patients with UICC stage IB disease received intravenous gemcitabine at a dose of 700 mg/m$^2$ biweekly, while patients with UICC stage II, IIA, IIB, IIIA, IIIB, IIIC, or IV disease received intravenous gemcitabine at a dose of 700 mg/m$^2$ on day 1 and oral S-1 at a dose of 50 mg/m$^2$ for seven consecutive days, followed by a 1-week pause of chemotherapy (i.e., one course of combined chemotherapy every two weeks). The plan was for all patients to receive ten cycles of adjuvant chemotherapy. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria scale (version 2.0). An additional course was delayed if toxicity of grade 3 or 4 was observed or if the patient's condition did not improve sufficiently to fit eligibility criteria. Neither external beam radiation nor intraoperative irradiation was given to any patient during the study period.

### Survival

Patients were followed regularly in outpatient clinics by undergoing a blood test, ultrasonography, and computed tomography twice a year for five years after surgery. Information on outcomes beyond five years after surgery was collected by telephone or personal interview. For patients who died, survival time after surgery and cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded.

Survival analyses on ten clinical factors (gender, age, tumor location, use of adjuvant chemotherapy, tumor differentiation, lymph node status, para-aortic lymph node status, surgical margin status, UICC pT factor, and UICC stage) were performed with univariate and multivariate methods. Clinicopathological factors were compared between patients with and without para-aortic lymph node metastasis. The median follow-up time after operation was 76 months (range = 2–216 months) for the 113 patients.

### Statistical analysis

The $\chi^2$ test or Fisher's exact test was used for comparison between the two groups. Survival curves were constructed based on the Kaplan–Meier method, and differences in survival curves were compared with a univariate log-rank (Mantel–Cox) test. Factors found to be significant on univariate analysis were subjected to multivariate analysis with a Cox proportional hazards model. A $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the Macintosh version of StatView v5.0 (SAS Institute, Cary, NC).

## Results

The 113 eligible patients included 76 men and 37 women (median age = 68 years; range = 35–86 years), and 45 patients (40%) were more than 70 years old. The 113 patients consisted of 6 with intrahepatic cholangiocarcinoma, 25 with hilar cholangiocarcinoma, 31 with distal cholangiocarcinoma, 19 with carcinoma of the gallbladder, and 32 with ampullary carcinoma. Depending on the location of the tumor and tumor spread, a wide variety of aggressive operative procedures was employed. Operative procedures performed are shown in Table 1. Major hepatectomy and pancreatoduodenectomy were performed in 34

**Table 1** Operative procedures in patients with biliary carcinoma

| | No. patients |
|---|---|
| Intrahepatic cholangiocarcinoma | 6 |
| Right hepatectomy | 2 |
| Left hepatectomy | 4 |
| Hilar chlangiocarcinoma | 25 |
| Right hepatectomy + CHx + BDR | 12 |
| Left hepatectomy + CHx + BDR | 6 |
| Left trisectionectomy + CHx + BDR | 1 |
| Right trisectionectomy + CHx + BDR | 3 |
| Right hepatectomy + CHx + PPPD | 1 |
| Left hepatectomy + CHx + PD | 1 |
| Hilar BDR + CHx | 1 |
| Distal cholangiocarcinoma | 31 |
| PPPD | 24 |
| PD | 6 |
| BDR | 1 |
| Carcinoma of the gallbladder | 19 |
| Right hepatectomy + CHx + BDR | 3 |
| Right trisectionectomy + CHx + BDR | 1 |
| (S4a + S5) hepatectomy + PD | 2 |
| (S4a + S5) hepatectomy + BDR | 1 |
| Gallbladder bed resection + PPPD | 2 |
| Gallbladder bed resection + BDR | 3 |
| Gallbladder bed resection | 2 |
| Cholecystectomy + BDR | 1 |
| Cholecystectomy | 4 |
| Ampullary carcinoma | 32 |
| PPPD | 32 |

*CHx* caudate lobectomy, *BDR* bile duct resection, *PPPD* pylorus-preserving pancreatoduodenectomy, *PD* conventional pancreatoduodenectomy

(30%) and 68 (60%) patients. Portal vein resection was performed in seven patients. No 30-day operative deaths occurred among the 113 patients. However, postoperative complications occurred in 43 patients (38%). Biliary fistula was the most common ($n = 18$), followed by pancreatic fistula ($n = 5$), surgical site infection ($n = 5$), enterocolitis ($n = 4$), chylous ascites ($n = 4$), intra-abdominal abscess ($n = 2$), and miscellaneous complications ($n = 5$). According to the Clavien–Dindo classification of surgical complications [27], these complications included grade I in 6 patients, grade II in 11 patients, grade IIIa in 25 patients, and grade IIIb in 1 patient. Postoperative chemotherapy was performed for 45 (40%) patients, including gemcitabine chemotherapy alone in 6 patients and gemcitabine plus S-1 chemotherapy in 39 patients. Pathologically, tumors were identified as well-differentiated adenocarcinoma in 60 patients (53%), moderately differentiated adenocarcinoma in 36 patients (32%), and poorly differentiated adenocarcinoma in 17 patients (15%). Ninety-nine patients (88%) had negative surgical margins. According to the TNM system, 17, 30, 7, 14, 41, and 4 patients had pT1, pT2, pT2a, pT2b, pT3, and pT4 tumors, respectively, and 1, 14, 13, 16, 9, 18, 6, 11, 9, 8, and eight patients were diagnosed with stage I, IA, IB, II, IIA, IIB, IIIA, IIIB, IV, IVA, and IVB disease, respectively. All patients with stage IV or IVB disease had para-aortic lymph node metastasis detected only by final pathological investigation, not by preoperative imaging examinations.

The median number of examined lymph nodes was 21 (range = 4–107), and the median number of examined para-aortic lymph nodes was 4 (range = 1–24). There were 51 cases (45%) with lymph node metastasis and 62 (55%) without lymph node metastasis. The number of involved lymph nodes ranged from 1 to 24 (median = 4). Para-aortic lymph node metastasis was found in 17 patients (15%). The number of involved para-aortic lymph nodes ranged from 1 to 14 (median = 2). All patients with para-aortic lymph node metastasis had regional lymph node metastasis.

Table 1 gives a comparison of clinicopathological factors between patients with and without para-aortic lymph node metastasis. Gender, age, tumor location, use of adjuvant chemotherapy, and UICC pT factor did not differ between the two groups. However, tumor differentiation ($P = 0.034$) and surgical margin status ($P = 0.007$) were significantly associated with para-aortic lymph node metastasis (Table 2).

Overall survival rates for the 113 patients were 82% at 1 year, 65% at 2 years, 58% at 3 years, and 52% at 5 years. Ten clinicopathological factors were investigated to determine their prognostic significance. The results of the log-rank test are shown in Table 3. Gender, age, tumor location, and adjuvant chemotherapy did not influence postoperative survival. Univariate analysis revealed that tumor differentiation ($P = 0.044$), lymph node metastasis ($P < 0.001$), para-aortic lymph node metastasis ($P = 0.007$), surgical margin status ($P < 0.001$), UICC pT factor ($P = 0.009$), and UICC stage ($P < 0.001$) were associated significantly with increased survival. These factors were entered into multivariate analysis with a Cox proportional hazards model, and negative lymph node metastasis ($P = 0.004$) and surgical margin status ($P = 0.035$) remained associated independently with longer survival. In contrast, para-aortic lymph node metastasis ($P = 0.323$) was not associated significantly with survival in the final multivariate model. UICC stage was not used as a dependent variable in the multivariate survival analysis to avoid confounding due to nodal status and UICC pT factor (Table 4).

The 5-year survival rates of patients with and without para-aortic lymph node metastasis were 24 and 57%, respectively. Survival rate of patients with para-aortic

**Table 2** Comparison of clinicopathological factors of patients with biliary carcinoma who did or did not have para-aortic lymph node metastasis

| | Para-aortic node metastasis | | |
|---|---|---|---|
| | Absent ($n = 96$) | Present ($n = 17$) | *P* |
| Gender | | | |
| Male | 67 | 9 | 0.172 |
| Female | 29 | 8 | |
| Age (years) | | | |
| <70 | 59 | 9 | 0.509 |
| ≥70 | 37 | 8 | |
| Location of the tumor | | | |
| Intrahepatic cholangiocarcinoma | 4 | 2 | 0.555 |
| Hilar cholangiocarcinoma | 22 | 3 | |
| Distal cholangiocarcinoma | 25 | 6 | |
| Carcinoma of the gallbladder | 16 | 3 | |
| Ampullary carcinoma | 29 | 3 | |
| Adjuvant chemotherapy | | | |
| Yes | 36 | 9 | 0.231 |
| No | 60 | 8 | |
| Tumor differentiation | | | |
| Well | 55 | 5 | 0.034 |
| Moderate, poor | 41 | 12 | |
| Surgical margin | | | |
| Positive | 8 | 6 | 0.007 |
| Negative | 88 | 11 | |
| UICC pT factor | | | |
| pT 1, 2, 2a | 47 | 7 | 0.554 |
| pT 2b, 3, 4 | 49 | 10 | |

*UICC* International Union Against Cancer

**Table 3** Univariate survival analysis of prognostic factors after resection of biliary carcinoma

| Factors | All patients | | | Node-positive patients | | |
|---|---|---|---|---|---|---|
| | No. patients | 5-year survival rate (%) | *P* | No. patients | 5-year survival rate (%) | *P* |
| Gender | | | | | | |
| Male | 76 | 53 | 0.881 | 29 | 29 | 0.663 |
| Female | 37 | 51 | | 22 | 29 | |
| Age (years) | | | | | | |
| <70 | 68 | 53 | 0.300 | 37 | 25 | 0.134 |
| ≥70 | 45 | 54 | | 14 | 44 | |
| Location of the tumor[a] | | | | | | |
| Intrahepatic cholangiocarcinoma | 6 | 60 | | 5 | 50 | |
| Hilar cholangiocarcinoma | 25 | 40 | | 10 | 25 | |
| Distal cholangiocarcinoma | 31 | 49 | | 15 | 22 | |
| Carcinoma of the gallbladder | 19 | 63 | | 10 | 31 | |
| Ampullary carcinoma | 32 | 55 | | 11 | 22 | |
| Adjuvant chemotherapy | | | | | | |
| Yes | 45 | 60 | 0.097 | 23 | 42 | 0.023 |
| No | 68 | 48 | | 28 | 20 | |
| Tumor differentiation | | | | | | |
| Well | 60 | 62 | 0.044 | 18 | 40 | 0.185 |
| Moderate, poor | 53 | 42 | | 33 | 24 | |
| Lymph node metastasis | | | | | | |
| Yes | 51 | 29 | <0.001 | | | |
| No | 62 | 72 | | | | |
| Para-aortic lymph node metastasis | | | | | | |
| Yes | 17 | 24 | 0.007 | 17 | 31 | 0.614 |
| No | 96 | 57 | | 34 | 24 | |
| Surgical margin | | | | | | |
| Positive | 14 | 0 | <0.001 | 13 | 0 | 0.011 |
| Negative | 99 | 59 | | 38 | 39 | |
| UICC pT factor | | | | | | |
| pT 1, 2, 2a | 54 | 65 | 0.009 | 17 | 42 | 0.169 |
| pT 2b, 3, 4 | 59 | 39 | | 34 | 19 | |
| UICC stage | | | | | | |
| I, IA, IB, II, IIA | 53 | 69 | <0.001 | | | |
| IIB, IIIA, IIIB, IV, IVA, IVB | 60 | 35 | | | | |

*UICC* International Union Against Cancer

[a] There were no significant differences among the five groups

lymph node metastasis was significantly worse than that of patients without para-aortic nodal involvement by log-rank test ($P = 0.007$). However, one patient with intrahepatic cholangiocarcinoma who exhibited para-aortic lymph node metastasis has survived more than 10 years after surgery without recurrence (Fig. 1a). In addition, survival of patients with para-aortic lymph node metastasis and that of node-positive patients without para-aortic lymph node metastasis were significantly worse than that of patients without nodal involvement ($P < 0.001$). However, no significant difference in survival of patients with or without para-aortic lymph node metastasis was found among patients who had nodal involvement ($P = 0.614$). The 5-year survival rates of node-negative patients, node-positive patients without para-aortic lymph node metastasis, and node-positive patients with para-aortic lymph node metastasis were 72, 31, and 24%, respectively. Median survival time of node-positive patients without para-aortic lymph node metastasis and node-positive patients with para-aortic lymph node metastasis were 14.3 and 14.7 months, respectively. Median survival time of node-negative patients could not be calculated because more than half of the patients are alive (Fig. 1b).

Among node-positive patients ($n = 51$), univariate analysis revealed that adjuvant chemotherapy ($P = 0.023$) and surgical margin status ($P = 0.011$) were associated

**Table 4** Multivariate survival analysis of prognostic factors after resection of biliary carcinoma

| Factors | Hazard ratio | 95% CI | *P* |
|---|---|---|---|
| All patients | | | |
| Model 1 | | | |
| Lymph node metastasis | | | |
| Yes | 2.97 | 1.42–6.24 | 0.004 |
| No | 1.0 | | |
| Surgical margin | | | |
| Negative | 1.0 | 1.07–5.59 | 0.035 |
| Positive | 2.44 | | |
| UICC pT factor | | | |
| pT 1, 2, 2a | 1.0 | 0.77–2.96 | 0.237 |
| pT 2b, 3, 4 | 1.50 | | |
| Tumor differentiation | | | |
| Well | 1.0 | 0.58–2.21 | 0.721 |
| Moderate, poor | 1.13 | | |
| Model 2 | | | |
| Surgical margin | | | |
| Negative | 1.0 | 1.39–7.68 | 0.007 |
| Positive | 3.26 | | |
| UICC pT factor | | | |
| pT 1, 2, 2a | 1.0 | 0.87–3.36 | 0.120 |
| pT 2b, 3, 4 | 1.71 | | |
| Para-aortic lymph node metastasis | | | |
| Yes | 1.51 | 0.67–3.39 | 0.323 |
| No | 1.0 | | |
| Tumor differentiation | | | |
| Well | 1.0 | 0.66–2.57 | 0.444 |
| Moderate, poor | 1.30 | | |
| Node-positive patients | | | |
| Surgical margin | | | |
| Negative | 1.0 | 1.11–5.53 | 0.027 |
| Positive | 2.48 | | |
| Adjuvant chemotherapy | | | |
| Yes | 1.0 | 1.02–5.00 | 0.045 |
| No | 2.26 | | |

*CI* confidence interval, *UICC* International Union Against Cancer

significantly with increased survival, although para-aortic lymph node metastasis did not affect patient survival ($P = 0.614$, Table 3). Moreover, adjuvant chemotherapy ($P = 0.045$) and surgical margin status ($P = 0.027$) were independent prognostic factors among patients with lymph node involvement (Table 4). The 5-year survival rates of node-positive patients who did or did not receive adjuvant chemotherapy were 42 and 20%, respectively (Fig. 2). However, adjuvant chemotherapy did not affect patient survival among patients with para-aortic lymph node metastasis ($P = 0.336$).

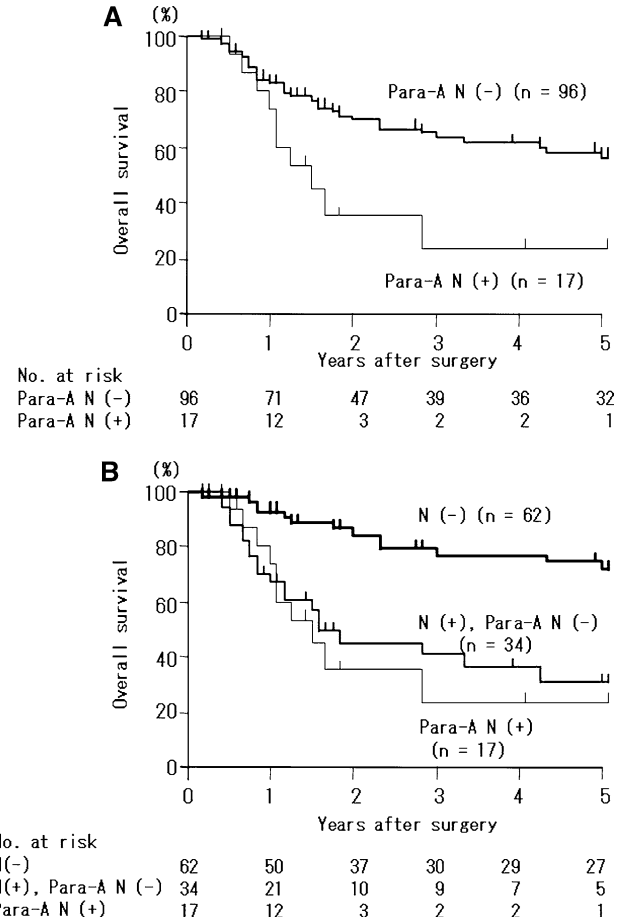


**Fig. 1** **a** Comparison of postoperative survival of patients with or without para-aortic lymph node involvement following resection for biliary carcinoma ($P = 0.007$). **b** Comparison of postoperative survival of patients who had no lymph node involvement, lymph node involvement without para-aortic involvement, and para-aortic lymph node involvement following resection for biliary carcinoma. N(−) vs. N(+), Para-A N(−), $P < 0.001$; N(−) vs. Para-A N(+), $P < 0.001$; N(+), Para-A N(−) vs. Para-A N(+), $P = 0.614$ (*N* lymph node involvement, *Para-A N* para-aortic lymph node involvement)

## Discussion

Lymph node metastasis frequently occurs in patients with biliary carcinoma. The rate of lymph node metastasis has been reported to be 20–62% in intrahepatic cholangiocarcinoma [9, 10, 18, 20], 18–47% in hilar cholangiocarcinoma [1, 2, 6, 10, 25], 25–58% in distal cholangiocarcinoma [3–5], 42–73% in carcinoma of the gallbladder [11, 12, 17, 19], and 31-50% in ampullary carcinoma [4, 13, 14, 16, 21, 22]. However, there have been few reports concerning the incidence of para-aortic lymph node metastasis because para-aortic lymph node dissection for patients with biliary carcinoma is not performed routinely worldwide. Studies on the incidence of para-aortic lymph node metastasis in biliary carcinoma were reported mainly from Japan. According to these reports, para-aortic lymph node metastasis occurred

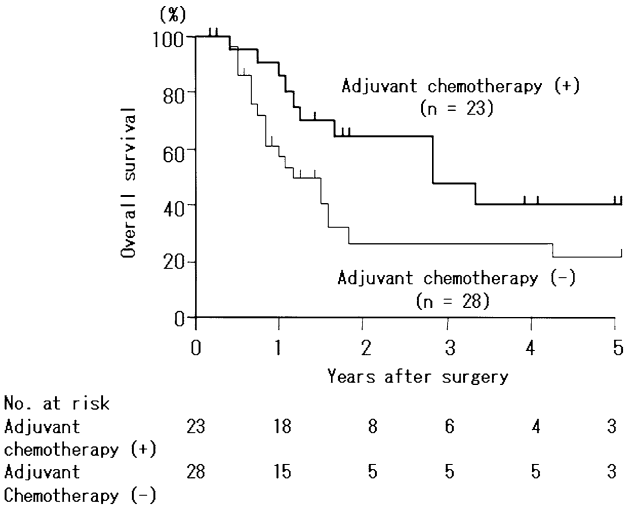


**Fig. 2** Comparison of postoperative survival in patients who did or did not receive adjuvant chemotherapy among node-positive patients following resection for biliary carcinoma ($P = 0.023$)

in 28% of patients with intrahepatic cholangiocarcinoma [18], 17% of patients with hilar cholangiocarcinoma [20], 19% of patients with distal cholangiocarcinoma [5], 19% of patients with carcinoma of the gallbladder [17], and 14% of patients with ampullary carcinoma [14]. The rate of para-aortic lymph node metastasis seemed to be 10–20% of patients with resected biliary carcinoma, although the results were based on a small number of patients (fewer than 50 patients). In this study, a total of 113 patients with biliary carcinoma were analyzed and the rates of lymph node metastasis and para-aortic lymph node metastasis were 45 and 15%, respectively, which was consistent with the prior reports.

In this series, patients with para-aortic lymph node metastasis had a significantly worse survival than those without para-aortic lymph node metastasis. However, survival of patients with para-aortic lymph node metastasis was similar to that of node-positive patients without para-aortic lymph node metastasis (5-year survival rate and median survival time, 24% and 14.7 months vs. 31% and 14.3 months, respectively). Moreover, para-aortic lymph node metastasis was not an independent prognostic factor among all patients and among patients with nodal involvement by multivariate analysis. Reports on long-term survival of patients with para-aortic lymph node metastasis in biliary carcinoma are scarce. Kondo et al. [19] reported that of 23 para-aortic node-positive patients with advanced gallbladder carcinoma who underwent surgical resection, their 1-year survival and median survival time were 43% and 5.8 months, respectively. They concluded that a sample biopsy of para-aortic nodes should be performed before starting radical resection. Other investigators also reported that there were no 5-year survivors of patients with para-aortic lymph node metastasis in biliary carcinoma, including carcinoma of the gallbladder [11, 17], ampullary carcinoma [22], and distal cholangiocarcinoma [16], although the numbers of patients with para-aortic lymph node metastasis in these reports were small (fewer than 10 patients). In contrast, Shinkai et al. [28] reported a case of gallbladder carcinoma with para-aortic lymph node metastasis who had survived more than seven years after the primary extended radical operation. In addition, Kitagawa et al. [20] reported that of 19 para-aortic node-positive patients with hilar cholangiocarcinoma, two patients survived for more than 5 years and the 5-year survival rate of patients with para-aortic lymph node metastasis was 12.3% They concluded that the fact that long-term survival is possible despite para-aortic lymph node metastasis encouraged the surgeons to perform an aggressive surgical procedure with extended lymph node dissection in selected patients with hilar cholangiocarcinoma. In this study, one para-aortic node-positive patient with intrahepatic cholangiocarcinoma had survived more than 10 years after surgery without recurrence [29]. Based on these results, we believe that in biliary carcinoma radical resection should be recommended for patients with para-aortic lymph node metastasis detected only by pathological examination, not by preoperative imaging examination, because long-term survival may be expected for the selected patients despite para-aortic lymph node metastasis. Further studies on a larger number of patients with para-aortic lymph node metastasis are needed.

Recently, new anticancer drugs, including gemcitabine [30], oxaliplatin [31], capecitabine [32], and S-1 [33] have been reported to have favorable anticancer effects on patients with unresectable biliary tract carcinoma. We have already reported that adjuvant gemcitabine plus S-1 chemotherapy improves survival significantly after surgery for biliary carcinoma [26]. In this study, adjuvant gemcitabine plus S-1 chemotherapy was used mainly for patients with advanced stage postoperatively. However, no significant difference in survival was found between patients who did and did not receive adjuvant chemotherapy by univariate survival analysis ($P = 0.097$). The reason is that patients who received adjuvant chemotherapy had significantly more advanced UICC stage cancer than those who did not ($P = 0.019$, data not shown). However, among patients with nodal involvement, survival of patients who received chemotherapy was significantly better than those who did not. Although a survival benefit was not found among patients with para-aortic lymph node metastasis (probably due to the small number of patients), we believe that adjuvant chemotherapy may contribute to improving survival of patients with para-aortic lymph node metastasis.

In the current study, pathologically curative resection (R0 resection) as well as adjuvant chemotherapy was an

independent prognostic factor among patients with nodal involvement. The result suggests that surgeons should carefully pursue R0 resection, even for node-positive patients with biliary carcinoma. We believe that R0 resection with lymph node dissection and adjuvant chemotherapy is mandatory to improve survival of node-positive patients with biliary carcinoma.

Dissection of para-aortic nodes is not technically difficult and it does not take much time to dissect the para-aortic connective tissue containing the lymph nodes between the levels of the celiac and inferior mesenteric arteries. Definite staging information can be obtained by this procedure without an increase in postoperative morbidity [20]. We will continue to perform dissection of para-aortic nodes in patients with biliary carcinoma in order to determine the prognostic significance of para-aortic lymph node metastasis in biliary carcinoma.

The limitations of this study are its retrospective, non-consecutive series format and the relatively small number of patients studied. There were only 17 patients with para-aortic lymph node metastasis in the current study. Further prospective studies on a larger number of patients with or without para-aortic lymph node metastasis are needed to confirm the results of this study. In addition, the eligible patients of this study included five different types of biliary carcinoma. Each type of biliary carcinoma has a slightly different prognosis. Further studies on the prognostic impact of para-aortic lymph node metastasis are also needed for each type of biliary carcinoma.

In conclusion, the prognosis of patients with para-aortic lymph node involvement is poorer than that of patients without para-aortic lymph node involvement in biliary carcinoma. However, survival of patients with para-aortic lymph node involvement is similar to that of node-positive patients without para-aortic lymph node involvement and long-term survival is expected in the selected patients with para-aortic lymph node involvement. Radical resection should not be abandoned for patients with para-aortic lymph node metastasis detected only by pathological examination, not by preoperative imaging examinations.

## References


1. Rea DJ, Munoz-Juarez M, Farnell MB et al (2004) Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. Arch Surg 139:514–523 discussion 523-525
2. Unno M, Katayose Y, Rikiyama T et al (2010) Major hepatectomy for perihilar cholangiocarcinoma. J Hepatobiliary Pancreat Surg 17:463–469
3. Murakami Y, Uemura K, Hayashidani Y et al (2007) Pancreatoduodenectomy for distal cholangiocarcinoma: prognostic impact of lymph node metastasis. World J Surg 31:337–342 discussion 343-344
4. Woo SM, Ryu JK, Lee SH et al (2007) Recurrence and prognostic factors of ampullary carcinoma after radical resection: comparison with distal extrahepatic cholangiocarcinoma. Ann Surg Oncol 14:3195–3201
5. Yoshida T, Matsumoto T, Sasaki A et al (2002) Prognostic factors after pancreatoduodenectomy with extended lymphadenectomy for distal bile duct cancer. Arch Surg 137:69–73
6. Hasegawa S, Ikai I, Fujii H et al (2007) Surgical resection of hilar cholangiocarcinoma: analysis of survival and postoperative complications. World J Surg 31:1256–1263
7. Miyazaki M, Kato A, Ito H et al (2007) Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? Surgery 141:581–588
8. Ebata T, Nagino M, Kamiya J et al (2003) Hepatectomy with portal vein resection for hilar cholangiocarcinoma: audit of 52 consecutive cases. Ann Surg 238:720–727
9. Uenishi T, Kubo S, Yamazaki O et al (2008) Indications for surgical treatment of intrahepatic cholangiocarcinoma with lymph node metastases. J Hepatobiliary Pancreat Surg 15:417–422
10. Guglielmi A, Ruzzenente A, Campagnaro T et al (2009) Intrahepatic cholangiocarcinoma: prognostic factors after surgical resection. World J Surg 33:1247–1254
11. Sasaki R, Itabashi H, Fujita T et al (2006) Significance of extensive surgery including resection of the pancreas head for the treatment of gallbladder cancer–from the perspective of mode of lymph node involvement and surgical outcome. World J Surg 30:36–42
12. Shimizu H, Kimura F, Yoshidome H et al (2007) Aggressive surgical approach for stage IV gallbladder carcinoma based on Japanese Society of Biliary Surgery classification. J Hepatobiliary Pancreat Surg 14:358–365
13. Kim RD, Kundhal PS, McGilvray ID et al (2006) Predictors of failure after pancreaticoduodenectomy for ampullary carcinoma. J Am Coll Surg 202:112–119
14. Duffy JP, Hines OJ, Liu JH et al (2003) Improved survival for adenocarcinoma of the ampulla of Vater: fifty-five consecutive resections. Arch Surg 138:941–950
15. Kurosaki I, Tsukada K, Hatakeyama K et al (1996) The mode of lymphatic spread in carcinoma of the bile duct. Am J Surg 172:239–243
16. Kayahara M, Nagakawa T, Ohta T et al (1997) Surgical strategy for carcinoma of the papilla of Vater on the basis of lymphatic spread and mode of recurrence. Surgery 121:611–617
17. Tsukada K, Kurosaki I, Uchida K et al (1997) Lymph node spread from carcinoma of the gallbladder. Cancer 80:661–667
18. Tsuji T, Hiraoka T, Kanemitsu K et al (2001) Lymphatic spreading pattern of intrahepatic cholangiocarcinoma. Surgery 129:401–407
19. Kondo S, Nimura Y, Hayakawa N et al (2000) Regional and para-aortic lymphadenectomy in radical surgery for advanced gallbladder carcinoma. Br J Surg 87:418–422
20. Kitagawa Y, Nagino M, Kamiya J et al (2001) Lymph node metastasis from hilar cholangiocarcinoma: audit of 110 patients who underwent regional and para aortic node dissection. Ann Surg 233:385–392
21. Moriya T, Kimura W, Hirai I et al (2006) Nodal involvement as an indicator of postoperative liver metastasis in carcinoma of the papilla of Vater. J Hepatobiliary Pancreat Surg 13:549–555
22. Sakata J, Shirai Y, Wakai T et al (2007) Number of positive lymph nodes independently affects long-term survival after resection in patients with ampullary carcinoma. Eur J Surg Oncol 33:346–351
23. Yonemori A, Kondo S, Matsuno Y et al (2009) Prognostic impact of para-aortic lymph node micrometastasis in patients with regional node-positive biliary cancer. Br J Surg 96:509–516
24. Sobin LH, Gospodarowicz MK, Wittekind C (eds) (2010) International Union Against Cancer (UICC): TNM classification of malignant tumors, 7th edn. Wiley-Blackwell, New York

25. Murakami Y, Uemura K, Sudo T et al (2009) Gemcitabine-based adjuvant chemotherapy improves survival after aggressive surgery for hilar cholangiocarcinoma. J Gastrointest Surg 13:1470–1479
26. Murakami Y, Uemura K, Sudo T et al (2009) Adjuvant gemcitabine plus S-1 chemotherapy improves survival after aggressive surgical resection for advanced biliary carcinoma. Ann Surg 250:950–956
27. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
28. Shinkai H, Kimura W, Sata N et al (1996) A case of gallbladder cancer with para-aortic lymph node metastasis who has survived more than seven years after the primary extended radical operation. Hepatogastroenterology 43:1370–1376
29. Murakami Y, Yokoyama T, Takesue Y et al (2000) Long-term survival of peripheral intrahepatic cholangiocarcinoma with metastasis to the para-aortic lymph nodes. Surgery 127:105–106
30. Penz M, Kornek GV, Raderer M et al (2001) Phase II trial of two-weekly gemcitabine in patients with advanced biliary tract cancer. Ann Oncol 12:183–186
31. André T, Tournigand C, Rosmorduc O et al (2004) Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 15:1339–1343
32. Patt YZ, Hassan MM, Aguayo A et al (2004) Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 101:578–586
33. Ueno H, Okusaka T, Ikeda M et al (2004) Phase II study of S-1 in patients with advanced biliary tract cancer. Br J Cancer 91:1769–1774