

The influence of the extent of lymph node on the prognosis for patients with intrahepatic cholangiocarcinoma undergone surgery

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INTRODUCTION

Intrahepatic cholangiocarcinoma (ICC) is a highly aggressive malignant tumor[1]. Most ICC patients have advanced-stage disease at diagnosis, and the 5-year overall survival (OS) rates are lower than 5%-10%[2]. ICC is prone to have lymph node metastasis (LNM). It has been reported that LNM is an independent risk factor for ICC prognosis. Surgical resection remains the mainstay of potentially curative therapy for ICC with median disease-free survival (DFS) time of 12–36 months reported in various studies. According to the latest NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancer (NCCN Guidelines[®]), distant (beyond the porta hepatic) LNM contraindicates surgery as it generally indicates advanced incurable disease[3]. However, it was reported that some ICC patients whose LNM beyond porta hepatic and even to para-aortic could still survive for a long time after radical surgery. So the relationship between the extent of LNM and prognosis is not clear[4]. Because the lymphatic outflow system of liver and biliary tract is multidirectional and complex, there has been no study directly investigating on the pathway of LNM in ICC. Few researches have studied the prognosis of ICC with LNM beyond the porta hepatic after radical surgery. In this article, the influence of LNM in different regions according to the NCCN guidelines on the prognosis of ICC patients undergoing radical resection were analyzed.

AIM

The aim of this study was to evaluate the effect of the extent of Lymph node metastasis (LNM) on the prognosis of intrahepatic cholangiocarcinoma (ICC) patients undergone resection.

METHOD

Patients and Study Design

Data on patients who underwent partial hepatectomy for ICC between September 1994 and November 2018 at two centers (the First Affiliated Hospital of Sun Yat-sen university and Sun Yat-sen university Cancer Center) were retrospectively analyzed. Inclusion criteria included the following: (1) initial ICC patients who received primary radical surgery (R0/1) in two centers above; (2) at least porta hepatic lymph node dissection during operation; (3) histopathologically proven ICC; (4) complete and available clinicopathologic data. Exclusion criteria were as follows: (1) palliative surgery; (2) perioperative mortality; (3) hilar or extrahepatic cholangiocarcinoma, including intrahepatic metastasis of extrahepatic cholangiocarcinoma, tumors of uncertain origin, metastatic liver cancer, combined hepatocellular-cholangiocarcinoma, combined with other malignant cancer; (4) recurrent ICC, Tis, Tx; (5) received prior treatment including neoadjuvant chemotherapy, radiotherapy, locoregional Therapy, et al; (6) no dissection of lymph node during operation, including lymph node sampling.

Definition of the extent of LNM

According to the NCCN guidelines, the extent of postoperative LNM confirmed by pathology was divided into the following three regions. Region A included hepatoduodenal ligament and common hepatic artery lymph nodes, Region B included gastrohepatic lymph nodes for left liver ICC and periduodenal and peripancreatic lymph node for right liver ICC. Region C included nodes beyond these regions above. Patients with no LNM, with LNM to Region A, Region B and Region C were defined as Group N0, Group 1, Group 2, and Group 3, respectively.

Multivariate COX regression analysis was performed to identify the prognostic factors for the overall survival (OS) and the recurrence-free survival (RFS). OS, RFS, costs and postoperative complications were compared between the two groups. We also investigated number, proportion and groups of LN+ in group B.

RESULTS

Tumor Recurrence and OS

The median RFS and OS were 4.89 months (95% CI=3.40, 7.97) and 12.79 months (95% CI=9.55, 19.70) for Group N1, and 9.12 months (95%CI=6.38, 19.83) and 27.07 months (95% CI=21.65, 43.30) for Group N0. Significant difference was found between Group N0 and N1 in RFS($p<0.001$) and OS($p=0.037$). However, there was no significant difference in RFS and OS between Group 1 and Group N0($p=0.104$ and $p=0.347$, Group 2 and Group N0 ($p=0.431$ and $p=0.404$). The median RFS and OS of Group 3 were 3.21 months (95%CI=1.72, 4.89) and 10.15 months (95%CI=8.00, 17.79). Significant difference could be observed between Group 3 and Group N0 in RFS ($p<0.001$) and OS ($p=0.002$). Based on the results above, we combined Group N0, 1 and 2 to a larger group, and a comparative study was then conducted between the newly-established group and the Group 3. The median RFS of the newly-established group was 8.60 months (95%CI=6.38, 11.87). Additionally, the median OS was 26.18 months (95% CI=18.98, 33.62). There was significant difference between the two groups in RFS ($p<0.001$) and OS ($p=0.037$).

Univariable and multivariable analysis of prognostic factors

When we compared Group 3 and Group N0, the multivariate analysis indicated that the grouping factor, which indicated the extent of LNM, was an independent risk factor of RFS (HR=2.43, 95%CI=1.32, 4.51, $p=0.005$). Furthermore, INR (HR=5.15, 95%CI=1.08, 24.49, $p=0.040$), CA199 (HR=3.35, 95%CI=1.54, 7.30, $p=0.002$), and vascular invasion (HR=2.15, 95%CI=1.01, 4.59, $p=0.047$) were also negative factors of RFS. But the grouping factor was not an independent risk factor ($p=0.178$) of OS in multivariable analysis although it was a negative factor (HR=2.30, 95%CI=1.34, 3.96, $p=0.002$) in univariable analysis. When we compared Group N0+1+2 with Group 3, the multivariable analysis revealed that the grouping factor (HR=2.46, 95%CI=1.47, 4.12, $p=0.001$), CA125 (HR=1.81, 95%CI=1.09, 2.98, $p=0.021$), CA199 (HR=2.77, 95%CI=1.51, 5.07, $p=0.001$), and tumor number (HR=1.94, 95%CI=1.10, 3.44, $p=0.023$) were significant risk factors for poor RFS. Univariable analysis showed that the grouping factor was a negative factor for OS (HR=1.90, 95%CI=1.18, 3.06, $p=0.008$), but in multivariate analysis, grouping factor was not an independent risk factors for OS ($p=0.061$).

CONCLUSIONS

In conclusion, ICC patients with LNM beyond the regional lymph nodes defined by NCCN, including gastrohepatic, periduodenal and peripancreatic lymph node, could still achieve good prognosis after radical surgery. However, when LNM beyond the range mentioned above, surgery should be carefully considered.

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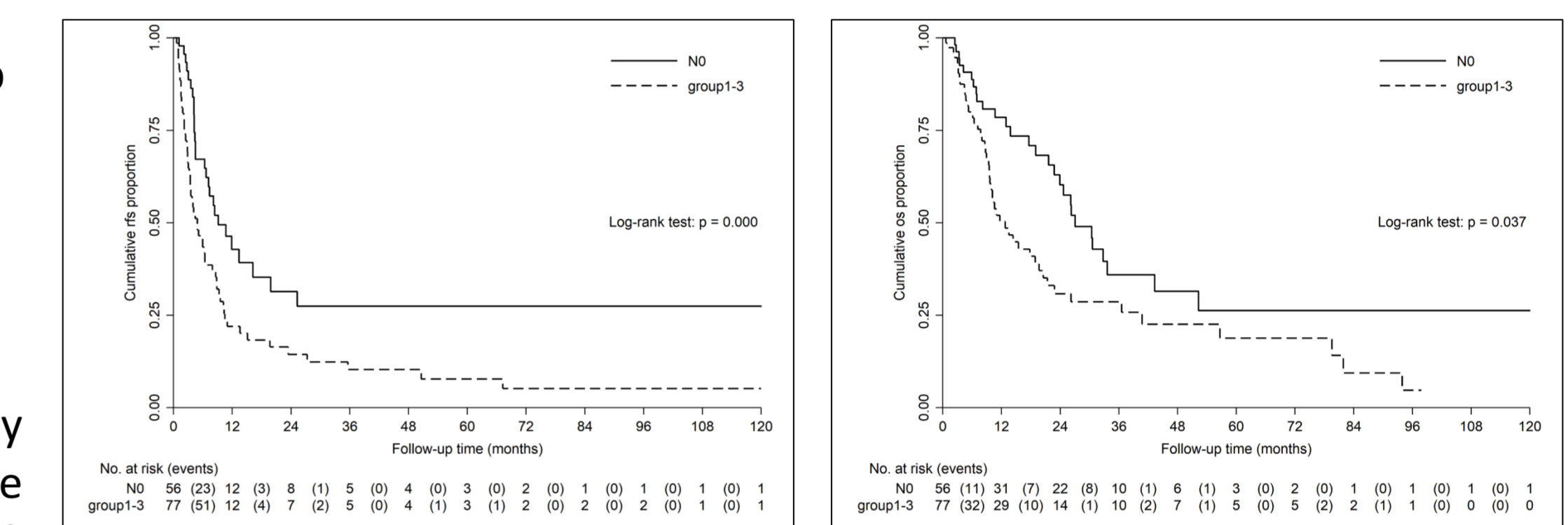


Fig. 1. Kaplan-Meier survival curves of patients in Group N0 (n=56) and Group N1 (n=77). A: RFS for patients in Group N0 and Group N1, $p<0.001$; B: OS for patients in Group N0 and Group N1, $p=0.037$.

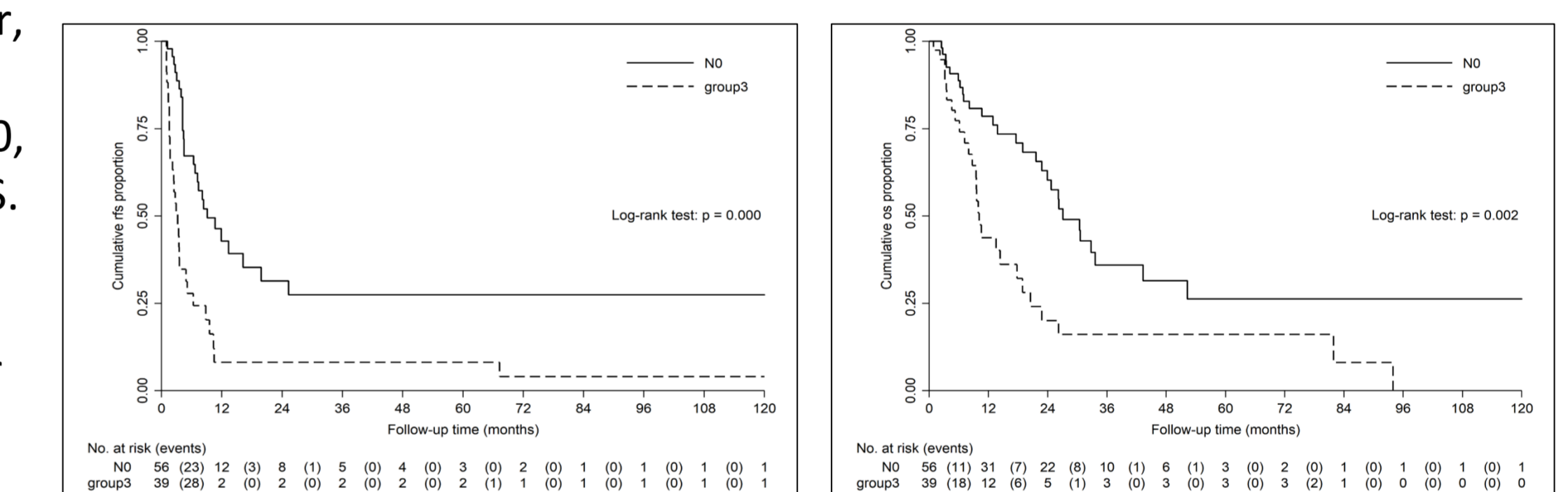


Fig. 2. Kaplan-Meier survival curves of patients in Group N0 (n=56) and Group 3 (n=39). A: RFS for patients in Group N0 and Group 3, $p<0.001$; B: OS for patients in Group N0 and Group 3, $p=0.002$.

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