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Prevalence and clinical significance of regional lymphadenectomy in patients with hepatocellular carcinoma

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Key words
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Abstract

Background: A limited amount of literature involves the clinical significance of regional lymphadenectomy during operations on hepatocellular carcinoma (HCC) patients. Our study aims to explore regional lymphadenectomy rate and node-positive rate, as well as their clinicopathological relevance and prognostic values in patients with HCC receiving liver resection (LR) and liver transplantation (LT).

Methods: Patients with HCC who received LR or LT and were diagnosed from 2004 to 2013 were retrieved from the Surveillance Epidemiology and End Results (SEER) database. A total of 6367 patients with staging and regional lymphadenectomy information was included.

Results: The regional lymphadenectomy rates were 14.3% and 28.6% in patients receiving LR and LT, respectively. Additionally, the rate of LT patients increased from 21.3% to 33.3% in the 2004–2013 time period. In patients with regional lymphadenectomy, node-positive rates were 8.4% and 0.9% in LR and LT patients, respectively. Regional lymphadenectomy was conducted relatively non-specifically in patients receiving LT compared with those receiving LR by analysing its clinicopathological relevance. Furthermore, regional lymphadenectomy did not improve prognosis in the general population or any subgroup.

Conclusion: There was a disparity between high regional lymphadenectomy rate and extremely low node-positive rate in patients with HCC receiving LT, which requires further improvement in future clinical practice.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. In the United States, the age-adjusted prevalence of HCC in 2010 was at least 6/100 000, which was predicted to increase in future due to a rising incidence of non-alcoholic steatohepatitis.[1] More than 50% of patients were diagnosed with HCC confined to the liver.[2] Surgical treatments, including liver resection (LR) and liver transplantation (LT) are the most prevalent and effective therapies for this kind of patient.[3]

The occurrence of regional lymph node metastases is 4–11% in patients with HCC.[4,5] Compared with distant metastases, lymph node metastases are comparatively localized, which is associated with poor prognosis, as well as more advanced tumour characteristics, such as multiple lesions, cancerous thrombi, higher AFP levels and distant metastases.[6–8] According to a report based on a Japanese nationwide survey, the prognosis of patients with lymph node metastatic HCC was similar to that of patients with locally advanced HCC, inferior to patients with stage I-III HCC and superior to patients with distant metastatic HCC.[9] In other words, the identification of positive lymph nodes is valuable for tumour staging

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and outcome prediction. Regional lymph node metastasis cannot be completely confirmed by imageological examination and operative exploration. In clinical practice, 1–2% of lymph node metastases are occult (histologically positive but clinically non-suspicious lymph nodes).[10] Some specialists advocate regional lymphadenectomy for primary and secondary hepatic malignancies.[11,12] However, this operation is accompanied by increased operating time and potential risks of complications. Thus Grobmyer *et al.* oppose conducting routine regional lymphadenectomy without clinical suspicion.[10]

Considering the existing controversies, it is of great significance to determine the prevalence and value of regional lymphadenectomy in clinical practice. In this study, based on the Surveillance Epidemiology and End Results (SEER) database, we analyse the prevalence and trend of regional lymphadenectomy, as well as the node-positive rates in patients with HCC receiving LR and LT. Additionally, we paid close attention to the clinicopathological relevance and prognostic value of regional lymphadenectomy.

Methods

Ethics statement

This study was deemed exempt from institutional review board approval by The First Affiliated Hospital of Sun Yat-sen University, and informed consent was waived. We conducted this study in accordance with the ethical standards of the World Medical Association Declaration of Helsinki.

Study population

Our study was based on information of patients with HCC registered the SEER database, which is a population-based cancer registry across several disparate geographic regions in the United States. The SEER research database of HCC from 1973 to 2013 (November 2015 submission) was retrieved for the present study.

HCC was identified with International Classification of Diseases for Oncology, third edition (ICD-O-3) site code C22.0 and histological type code 8170-8175. The patient screening process is shown in Figure S1. To begin with, 83 565 patients pathologically diagnosed with HCC were retrieved from the SEER database. Among them, only those with complete information for American Joint Committee on Cancer (AJCC) 6th tumour-node-metastasis (TNM) classification were included (n = 39 790, all diagnosed from 2004 to 2013). The AJCC 7th TNM classification was not adopted because it started in 2010, which might result in fewer enrolled patients. Then, patients who receiving LR or LT were further selected (n = 6433). Finally, those without information on regional lymphadenectomy (no/yes) were excluded. Therefore, 6367 patients were included as the final study population.

Baseline characteristics of the study population are shown in Table S1. The majority of patients were males (n = 4715, 74.1%), with a median age of 60 years. Additionally, 53.4% (n = 3398) of patients were classified as T1. A total of 98 (1.5%) patients were diagnosed with regional lymph node metastases. Among them, 60/98 (61.2%) were confirmed by regional lymphadenectomy and pathological diagnosis (based on frozen section or post-operative pathological results). The others might have been diagnosed with imageological examination and intra-operative exploration (no information about their diagnostic methods in the SEER). A total of 106 (1.7%) patients had distant metastases, and 21 (0.3%) patients suffered from both regional lymph nodes and distant metastases. There were 3766 (59.1%) patients receiving LR and 2601 (40.9%) patients undergoing LT. In addition, the majority of patients (n = 3779, 68.3%) had only one lesion.

Statistical analyses

The statistical analyses were performed with SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The comparisons of demographic and clinicopathological characteristics between patients with and without regional lymphadenectomy were conducted using chi-squared tests or Kruskal–Wallis H tests. Overall survival (OS) was defined as the time interval between diagnosis of HCC and death of any cause. Disease-specific survival (DSS) was the time interval between diagnosis of HCC and death attributed to HCC. Univariate and multivariate Cox proportional hazards regression models were adopted to evaluate the prognostic value of regional lymphadenectomy (no/yes) on OS and DSS. The hazard ratio (HR) and 95% confidence interval (CI) were estimated by the Cox proportional hazard models. Adjusted survival curves of DSS and OS were plotted by the Kaplan–Meier method and compared by log-rank test. A likelihood ratio test was applied to test the interactions between regional lymphadenectomy (no/yes) and clinicopathological characteristics on OS and DSS. P values ≤0.05 were considered to be statistically significant.

Results

Prevalence of regional lymphadenectomy and node-positive rates

Of all patients, 20.1% (1281/6367) received regional lymphadenectomy. Specifically, the rate of patients undergoing regional lymphadenectomy was 14.3% (538/3766) in the LR group, while 28.6% (743/2601) of LT patients underwent regional lymphadenectomy. During 2004–2013, the rate of regional lymphadenectomy maintained stability, ranging from 18.5% to 23.1%. For LR patients, regional lymphadenectomy rate decreased slightly from 17.0% in 2004 to 12.8% in 2013. However, the rate increased from 21.3% in 2004 to 33.3% in 2013 for the LT group. Details are shown in Figure 1a.

Additionally, the node-positive rate was only 4.1% (52/1281) in all patients with regional lymphadenectomy. Furthermore, the node-positive rate was 8.4% (45/538) and 0.9% (7/743) in LR and LT group, respectively. No significant change to node-positive rate was found in either group during 2004–2013. Details are shown in Figure 1b.

Characteristics associated with regional lymph node metastasis

Although a higher proportion of LT patients received regional lymphadenectomy compared with the LR group (LT versus LR: 28.6% versus 14.3%), their node-positive rate was grossly low (LT versus LR: 0.9% versus 4.1%). We further analysed their clinicopathological features to identify what kind of LT patients are more likely to suffer from regional lymph node metastasis (Table S2). We found

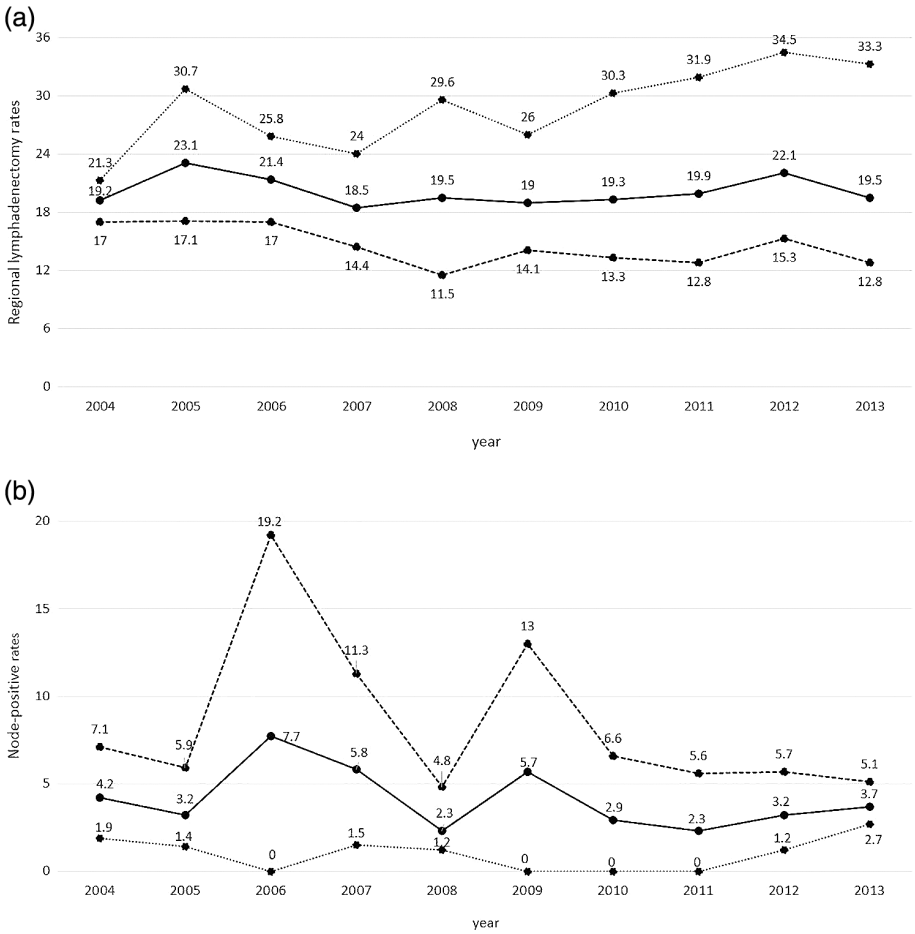

Fig. 1. (a) The trend of regional lymphadenectomy rates in hepatocellular carcinoma (HCC) patients receiving liver resection and liver transplantation during 2004–2013. (b) The trend of node-sampling positive rates in HCC patients receiving liver resection and liver transplantation during 2004–2013. (—●—), General; (--●--), Liver resection; (···●···), Liver transplantation.

that T classification, M classification and tumour size were associated with regional lymph node metastases. Patients with T3-4 classification (2.8%) and larger tumour size (>3 cm, 1.3%) had significantly higher node-positive rates, while node-positive rate in patients with T1 classification (0.5%) and smaller tumour size (≤3 cm, 0.5%) was significantly lower.

Characteristics associated with regional lymphadenectomy

In order to distinguish patients who were most likely to receive regional lymphadenectomy, we analysed the association between regional lymphadenectomy (no/yes) and patient characteristics (e.g. baseline and clinicopathological features) (Table S3).

In general, younger age (≤60 years old) ($P < 0.001$), more advanced T classification ($P < 0.001$), regional lymph node metastases ($P < 0.001$), distant metastases ($P = 0.03$) and more than one lesion ($P < 0.001$) were related to higher rates of regional lymphadenectomy. Furthermore, patients who received LT were more likely to receive regional lymphadenectomy ($P < 0.001$).

Besides, LR patients with younger age (≤60 years) ($P < 0.001$), more advanced T classification ($P < 0.001$), regional lymph node metastases ($P < 0.001$), distant metastases ($P = 0.001$), higher tumour grade ($P < 0.001$) and more than one lesion ($P = 0.03$) tended to carry on regional lymphadenectomy. However, in LT patients, only more advanced T classification ($P = 0.02$) and regional lymph node metastases ($P = 0.01$) were associated with higher regional lymphadenectomy rates. Put another way, compared with LR patients, LT patients seemed to have more randomized regional lymphadenectomy.

Prognostic value of regional lymphadenectomy on OS and DSS

In univariate analyses, regional lymphadenectomy was related to superior OS (HR (95% CI): 0.87 (0.80–0.98), $P = 0.02$). Other significant prognostic factors for OS included age ($P < 0.001$), TNM stage ($P < 0.001$), surgery type ($P < 0.001$), tumour grade ($P < 0.001$), tumour size ($P < 0.001$) and lesion number ($P < 0.001$). However, regional lymphadenectomy was not an independent prognostic factor for OS (HR (95% CI): 0.94 (0.83–1.07), $P = 0.37$) after being adjusted by above prognostic factors in multivariate analyses.

Similarly, regional lymphadenectomy was related to superior DSS (HR (95% CI): 0.84 (0.74–0.96), $P = 0.01$) in univariate analyses. Other significant prognostic factors for DSS included age ($P < 0.001$), TNM stage ($P < 0.001$), surgery type ($P < 0.001$), tumour grade ($P < 0.001$), tumour size ($P < 0.001$) and lesion number ($P < 0.001$). After adjustment for the aforementioned prognostic factors in multivariate analyses, regional lymphadenectomy was not an independent prognostic indicator for DSS (HR (95% CI): 0.89 (0.75–1.05), $P = 0.15$).

Detailed information about univariate and multivariate analyses of OS and DSS is shown in Table S4. In addition, the prognostic

value of regional lymphadenectomy on OS and DSS was examined by multivariate analyses in subgroups (Figure S2a for OS and Figure S2b for DSS). No impact of regional lymphadenectomy was found on OS or DSS in any subgroup. No significant interactions were found between regional lymphadenectomy and other clinicopathological characteristics on OS and DSS.

Discussion

In our present study, we reported the prevalence and trend of regional lymphadenectomy in patients with HCC receiving LR and LT during 2004–2013 in the United States. At the same time, node-positive rates in patients receiving LR and LT were released, respectively. In addition, we found that patients with more advanced cancer characteristics were inclined to receive regional lymphadenectomy. Nevertheless, regional lymphadenectomy had no role in improving patients' survival.

On the grounds of most articles, the occurrence of regional lymph node metastases is no more than 5% in patients with HCC,[13,14] though regional lymph node metastases are common for intra-hepatic cholangiocarcinoma (25%, 27% and 45%) and some secondary liver cancers, such as liver metastases of colorectal cancer (12%, 27% and 28%).[15–20] In a large retrospective study of 968 Chinese patients with HCC who received LR, regional lymph node metastases were found in 49 (5.1%) patients.[8] According to another study, based on 14 872 Japanese patients with HCC treated with LR, the rate of regional lymph node metastases was 1.2%.[9] Nonetheless, the regional lymph node metastases rate (8.4%) in our LR group was slightly higher than that in the Chinese and Japanese population. Whether patient selection, aetiological factors or ethnic differences are responsible for the disparity in lymph node metastasis still needs further investigation.

As announced in a meta-analysis, which included 606 patients with HCC receiving LT from 1990 to 2004, the positive rate of regional lymphadenectomy was 9.1%, but the dynamic change trend of it was undeclared recently. As far as we know, our study updated recent data on the node-positive rate in patients with HCC undergoing LT, which was extremely low at 0.9%.

Regional lymph node metastasis was an inferior prognostic indicator for patients with HCC receiving LR and LT.[6,8,9,21,22] In light of relevant works of literature, Ercolani *et al.* advocated routine regional lymphadenectomy after LR.[11] Sotiropoulos *et al.* also recommended regional lymphadenectomy during LT.[21] However, we found that, in patients with HCC receiving LT from 2004 to 2013, their regional lymphadenectomy rate rose while node-positive rate remained extremely low. By contrast, the regional lymphadenectomy rate in patients receiving LR was lower, but the node-positive rate was still acceptable.

By analysing the clinicopathological relevance of regional lymphadenectomy (no/yes), we found regional lymphadenectomy was more likely to be administered to LR patients with more aggressive and advanced tumours, including more advanced T classification, regional lymph node metastases, distant metastases, higher tumour grade, larger tumours size and multiple lesions. However, regional lymphadenectomy was only related to more advanced T classification and regional lymph node metastases in LT patients. One possible explanation for the above phenomenon was that indication of regional lymphadenectomy was relatively non-specific in LT patients. Another potential reason was that surgeons needed to resect certain swollen lymph nodes so that they could expose the hilar anatomical structures fully during LT. Lymph nodes enlargement was frequently presented in patients with hepatitis virus-related liver cirrhosis, which resulted from chronic inflammation.[23,24] Aiming to improve this situation, we analysed the clinicopathological association of regional lymph node metastases in LT patients, on whom regional lymphadenectomy should be preferentially performed. We found patients with T3-4 classification and larger tumour size (>3 cm) suffered from higher rates of lymph node metastases. On the other hand, regional lymphadenectomy should be performed on patients with T1 classification and smaller tumour size after careful consideration, since their node-positive rate was significantly lower.

As previously mentioned, the regional lymphadenectomy rate is relatively high in patients with HCC receiving LT. But the effect of regional lymphadenectomy on prognosis is unclear. One of the theoretically possible benefits is that regional lymphadenectomy may be accompanied by removal of regional lymphatic micrometastases, which might improve patients' survival. However, in accordance with our study, regional lymphadenectomy played no role in ameliorating OS or DSS of the general population or any subgroup. Reports from other research centres claimed that occult lymph node metastases were found in merely 1–2% patients.[10] Although there were no reports about the prognostic impact of regional lymphadenectomy, complete lymphadenectomy was proven to have no influence on reducing tumour recurrence or improving prognosis in operable HCC by other researchers.[8,25]

To our knowledge, regional lymphadenectomy had no prognostic benefit for patients with HCC, and it was conducive to acquiring a more accurate N classification for only 0.9% of LT patients. How about the risk of regional lymphadenectomy? Grobmyer *et al.* found that 2% of intra-operative complications did relate with regional lymphadenectomy, including injuring portal vein branch and causing duodenal diverticulum.[10] The risk of intra-operative and post-operative complications owing to regional lymphadenectomy could be even higher in patients with portal hypertension secondary to liver cirrhosis. Apart from that, an extra-regional lymphadenectomy would result in a prolonged cold ischaemic time. Taking all these factors into consideration, our study suggests that a more selective strategy should be set up for LT patients.

There are several limitations in our present study. First of all, this study was based on the SEER database, whose heterogeneity might have a particularly negative influence on our study. For example, as shown in the SEER database, 11 patients with extra-hepatic metastasis and 20 patients with lymph node metastasis received LT, which obviously violated the criteria for selecting transplant candidates. In addition, the indication of regional lymphadenectomy was not recorded and might also be heterogeneous. We could only conclude that patients with some clinicopathological characteristics were more inclined to receive regional lymphadenectomy by association analyses. Secondly, several considerable important results from clinical and laboratory tests, such as liver function and portal hypertension were absent. Most importantly, the lack of data for intra-operative and post-operative complications restricted the evaluation of regional

lymphadenectomy's risk. Nevertheless, this study sheds light on the prevalence and clinical value of regional lymphadenectomy inoperable HCC patients in real-world clinical practice. The disparity between high regional lymphadenectomy rate and extremely low node-positive rate in those receiving LT was revealed, which calls attention for investigations to improve this situation.

Conclusion

In conclusion, the regional lymphadenectomy rate in patients with HCC receiving LT was higher than that in the LR group, and it kept increasing during from 2004 to 2013. However, the node-positive rate in LT patients was extremely low (0.9%). Compared with the LR group, LT patients seemed to receive more unselected regional lymphadenectomy, and regional lymphadenectomy played no part in improving the prognosis of the whole population or any subgroup. More effort needs to be made to improve the disparity between high regional lymphadenectomy rate and extremely low node-positive rate in patients with HCC receiving LT.

Conflicts of interest

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. The flow chart for selection of study population. Abbreviations: SEER, Surveillance, Epidemiology, and End Results; ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; AJCC, American Joint Committee on Cancer; TNM, tumour-node-metastasis.

Figure S2. Subgroups analyses for the prognostic value of regional lymphadenectomy (yes/no) on (a) overall survival (OS) and (b) disease-specific survival (DSS).

Table S1. Baseline characteristics of the study population.

Table S2. The association between regional lymph nodes metastasis and patients' characteristics in those receiving liver transplantation.

Table S3. Clinicopathological relevance of regional lymphadenectomy in patients with hepatocellular carcinoma.

Table S4. Univariate and multivariate analysis for the impact of regional lymphadenectomy on DSS and OS in patients with hepatocellular carcinoma.