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ORIGINAL ARTICLE

Hilar lymph nodes sampling at the time of liver transplantation for hepatocellular carcinoma: to do or not to do?

Meta-analysis to determine the impact of hilar lymph nodes metastases on tumor recurrence and survival in patients with hepatocellular carcinoma undergoing liver transplantation

Georgios C. Sotiropoulos,[1] Massimo Malagó,[1] Ernesto P. Molmenti,[1] Christian Lösch,[2] Hauke Lang,[1] Andrea Frilling,[1] Christoph E. Broelsch[1] and Markus Neuhäuser[2]

1 Department of General, Visceral and Transplantation Surgery, University Hospital Essen, Essen, Germany
2 Institute for Medical Informatics, Biometry and Epidemiology, University Hospital Essen, Essen, Germany

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Correspondence
Dr Georgios C. Sotiropoulos, Department of General, Visceral and Transplantation Surgery, University Hospital Essen, Hufelandstr. 55, D-45122 Essen, Germany. Tels.: +49 201 723 1102, +49 174 2144056; fax: +49 201 723 1142; e-mail: georgios.sotiropoulos@uni-essen.de

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Summary

The purpose of this study was to evaluate the impact of tumor-positive hilar lymph nodes (LN) on tumor recurrence and survival in patients with hepatocellular carcinoma (HCC) undergoing liver transplantation (LT). A computer search of the Medline database was carried out. The outcome of patients with positive hilar LN (study group) was compared with that of patients with negative LN (reference group). Five clinical studies evaluating tumor recurrence after LT for HCC according to hilar LN status were identified. Five further clinical studies evaluated patients' survival in reference to LN metastases. The test of heterogeneity for each comparison revealed no significant differences (exact $P = 0.4638$). A significant correlation between tumor-positive LN and tumor recurrence was shown (exact estimation of common odds ratio by 10.44, 95% confidence interval of 3.431–38.59). Furthermore, data analyses using the Fisher-combination test regarding patient survival in the two groups showed a statistical difference ($P < 0.0001$). The negative prognostic value of hilar LN metastasis for both tumor recurrence and survival was confirmed by this analysis. Given the ever-present diagnostic dilemma associated with enlarged hilar LN, especially in hepatitis C-positive patients, hilar LN sampling during LT for HCC could better define patients at risk.

Introduction

Hilar lymph node (LN) involvement in cases of hepatocellular carcinoma (HCC) constitutes a contraindication for liver transplantation (LT). As such, patients suspected of having LN metastases during the pretransplant radiologic evaluation are being removed from waiting lists. However, this situation is complicated by the frequent presence of LN enlargement due to chronic inflammation in cases of hepatitis C-induced cirrhosis [1–8]. The differential diagnosis of LN swelling in patients with HCC arising in hepatitis C cirrhosis remains difficult [9–15], and the decision of whether to proceed with a LT has been considered only in transplant centers performing live donor LT for extended tumor indications [16]. In such cases, the option of an elective surgery with evaluation of LN by frozen sections of resected LN facilitates the decision making.

The goal of our study was to determine the prognostic significance of hilar LN metastases on patient survival and tumor recurrence, and to evaluate the significance of hilar LN sampling at the time of LT.

Materials and methods

Literature search

A computer search of the Medline database for the years 1985–2005 was carried out using the MeSH headings: 'hepatocellular carcinoma', 'liver transplantation', 'tumor recurrence', 'lymph nodes', and 'tumor staging'. The combined set was limited to English language publications on human subjects. All titles and abstracts were scanned, and appropriate citations reviewed. Consultation with a content expert and a manual search of the bibliographies of relevant papers was also carried out to identify trials for possible inclusion.

Inclusion criteria

Inclusion criteria for this analysis were clinical studies of any size on LT for HCC. Special emphasis was placed on the effect of LN metastasis on tumor recurrence and patient survival. Outcome of patients with positive hilar LN (study group) was compared with that of patients with no LN metastases (reference group).

Data collection

Critical appraisal and data extraction were conducted independently by the authors, and discrepancies resolved by consensus. In instances of multiple studies from a single institution, the most recent or more informative publication was chosen.

Analyses

Comparisons of results across studies were pooled for tumor recurrence and mortality. All analyses were conducted on a personal computer using Review Manager 3.0 (The Cochrane Collaboration, Software Update, Oxford, UK). A fixed effects model was applied. Statistical analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA) and StatXact (Cytel Software Corp., Cambridge, MA, USA). The summary statistic used was the odds ratio, which represents the odds of an event (tumor recurrence, mortality) occurring in the group of patients with positive hilar LN divided by odds of the control group. Odds ratios >1 display the higher risk in the tumor-positive LN group, and the point estimate of the odds ratio is considered statistically significant at the alpha = 0.05 level only if the 95% confidence interval (95% CI) does not include the vertical bar at 1. Any value lying within the 95% CI is considered to be consistent with the data, in the sense that it cannot be rejected at the 0.05 level. Because the sample size was relatively small in some studies exact statistical methods were applied [17]. The exact CI for the odds ratio of a single study was computed according to Cox [18]. Homogeneity of odds ratios across different studies was tested using the exact homogeneity test [19]. If this test was not significant, no evidence for heterogeneity was considered, i.e. for systematic differences between the studies. In that case a CI for the common odds ratio was calculated [20].

Results

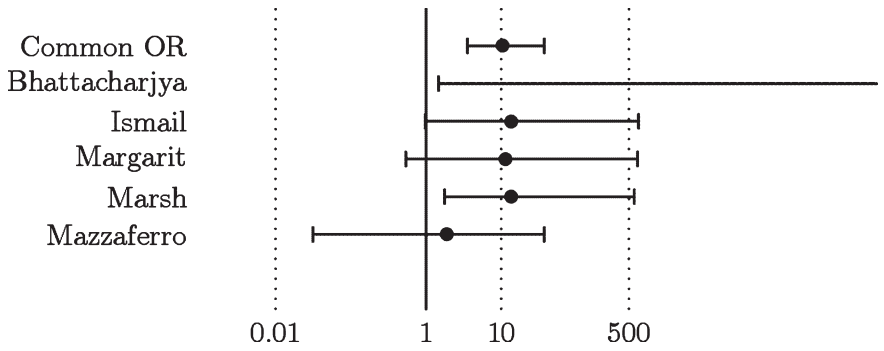
Among 34 retrospective clinical studies screened [21–54], five fulfilled the criteria described in *Materials and methods* [21–25]. The studies dated from 1990 to 2004 and contained from 20 to 178 patients, yielding a total of 397 patients for this analysis. Ismail *et al.* reported 10 recurrences after LT for HCC, six of them in the presence of tumor-positive LN. As the Milan criteria for LT for HCC had not been yet established, Ismail's study encompassed patients with more advanced tumor stages. Mazzaferro *et al.* reported a total of 17 post-transplant tumor recurrences in their series of 80 patients, one of them in the study group. Seventy-one further cases of tumor recurrence were referred by Marsh *et al.*, the majority of them ($n = 63$) in patients without LN tumor metastases. A total of 19 cases of post-transplant tumor recurrence were reported in the series of Margarit *et al.* and of Bhattacharjya *et al.*, with two cases of recurrences in the study group for each of the studies. Characteristics of the studies are summarized in Table 1.

Evaluation of the data extraction showed 100% agreement among the reviewers. Study-specific and common odds ratios for the outcomes are displayed in Fig. 1. The estimates of effect size (odds ratio of LN infiltration versus the control group) on recurrence was 10.44 (exact estimation of common odds ratio, 95% CI 3.431–38.59), showing a significant correlation between LN infiltration during LT and recurrence of HCC. The width of the horizontal bars reflects the 95% CI expressed on a logarithmic scale. The test of heterogeneity for each comparison revealed no significant differences between the studies (exact $P = 0.4638$), permitting pooling of the data using a fixed effects model. The point estimates of odds ratio for recurrence ranged from 1.906 to infinity, suggesting that LN infiltration is associated with an increased recurrence rate.

Between the 34 studies screened, five retrospective clinical studies that evaluated patient survival after LT for HCC according to the hilar LN status were identified [21, 26–29]. The studies dated from 1990 to 2004 and contained from 20 to 387 patients, yielding a total of 606 patients for this analysis (Table 2). Selby *et al.* showed a statistically worse patient survival ($P = 0.0054$) in the presence of LN metastases (mean survival of

Table 1. Characteristics of clinical studies evaluating tumor recurrence after liver transplantation for hepatocellular carcinoma according to lymph nodes (LN) status in the liver hilum.

	Ismail [21]	Mazzaferro [22]	Marsh [23]	Margarit [24]	Bhattacharjya [25]	Total
Year	1990	1994	1997	2002	2004	
Total number of subjects	20	80	178	89	30	397
Study group (positive LN)	7	3	9	3	2	24
Reference group (negative LN)	13	77	169	86	28	373
Recurrences in study group	6	1	8	2	2	19
Recurrences in reference group	4	16	63	13	2	98



Study	OR	Lower bound of 95% CI	Upper bound of 95% CI
Common OR	10.44	3.431	38.59
Bhattacharjya	Infinity	1.422	Infinity
Ismail	13.5	0.9488	687.9
Margarit	11.23	0.525	671.2
Marsh	13.46	1.715	602.7
Mazzaferro	1.906	0.0304	38.46

Figure 1 Odds ratios and CI of clinical studies evaluating tumor recurrence after liver transplantation for hepatocellular carcinoma according to hilar lymph nodes status. Meta-analysis resulted to a common odds ratio of 10.44.

Table 2. Characteristics of clinical studies evaluating patient outcome after liver transplantation for hepatocellular carcinoma according to lymph nodes (LN) status in the liver hilum.

	Ismail [21]	Ringe [26]	Selby [27]	Klintmalm [28]	Yedibela [29]	Total
Year	1990	1991	1995	1998	2004	
Total number of subjects	20	61	105	387	33	606
Study group (positive LN)	7	12	9	25	2	55
Reference group (negative LN)	13	49	96	362	31	551
P-value	0.5627	0.0004	0.0054	0.0014	0.6012	<0.001

10.5 months) when compared with a mean survival of 49.7 months of the reference group (negative LN). Ringe *et al.* demonstrated also a worse patient survival ($P = 0.0004$) in the presence of LN metastasis. In their series, the median survival of 1.5 months and the 5-year survival of 0% were statistically inferior to the corresponding median survival of 10.8 months and 5-year survival of 19% in cases of tumor-negative LN. Klintmalm also showed a significantly better patient survival ($P = 0.0014$) in the absence of LN metastases (5-year survival of about 45%) when compared with tumor-positive LN (5-year survival of about 25%). In the series of Ismail *et al.* median patient survival was also better in the reference group (13 months for tumor-negative and 8 months for tumor-positive LN, respectively). Note that in the series of Yedibela *et al.*, the 5-year survival was 100% for patients

with positive LN ($n = 2$) and 77% in the group of 31 patients with no LN metastases. However, sample sizes were small and the difference is far from being significant ($P = 0.6012$).

Data analyses using the Fisher-combination test [55,56] yield $\chi^2 = 41.40$ (d.f. = 10), which corresponds to a P-value <0.0001. That corresponds to a significant correlation between LN infiltration during LT for HCC and decreased survival.

Discussion

There are only sporadic reports addressing the negative prognostic influence of LN metastases in LT for HCC. The prognostic value of hilar LN metastases in LT for HCC and the worth of LN sampling are tasks of great importance that have not been previously reviewed systematically. In many cases, transplant surgeons do not perform a hilar LN sampling during the hepatectomy stage of LT. Reasons for such approach include: (i) The LN enlargement in cases of hepatitis C-induced liver cirrhosis cannot usually be distinguished clinically or radiologically from tumor involvement [9–15, 57], (ii) LT is an 'emergency-not scheduled' operation and in many transplant centers there may be no pathologist on duty during the night or week-end to perform frozen sections, (iii) 'Time is running' – a rapid hepatectomy is preferred in order to minimize the cold ischemic time.

The literature on LT for HCC shows shifting patterns throughout the past decades in reference to LN involvement [21–54]. Whether this is the result of improved selection (small tumors in early stages) or an abandonment of LN sampling during LT remains unclear.

Multiple reports address the enlargement of hilar LN in cases of hepatitis C cirrhosis, and its correlation with the severity of hepatitis infection. The mechanism of portal lymphadenopathy in patients with chronic hepatitis is still unclear, but appears to be related to the viral replication within the liver and the immune-mediated inflammatory response of the host [2–8].

Enlarged LN in the liver hilum are sonographically detectable in almost all patients with primary biliary cirrhosis. The total peri hepatic LN volume in patients with primary biliary cirrhosis reflects the histologic stage, i.e. larger LN are observed in more advanced disease [58–59].

Our systematic review of the literature and meta-analysis of clinical studies on LT for HCC showed that hilar LN metastases in cases of LT for HCC constitute a significant negative prognostic factor both for early post-transplant recurrence (common odds ratio by 10.44, 95% CI 3.431–38.59) as well as for patient survival ($P < 0.0001$). Given the diagnostic and operative dilemma of pathologically enlarged hilar LN in patients with HCC and hepatitis C or secondary biliary cirrhosis, and the significantly negative prognostic value of positive hilar LN on post-transplant tumor recurrence and patient survival, hilar LN sampling during LT for HCC could better define patients at risk and its routine appliance may need reconsideration in the era of transplant surgery.

According to our experience as well as to the results of this meta-analysis, systematic hilar lymphadenectomy during LT for HCC should routinely be undertaken, especially in the context of coexisting hepatitis C or secondary biliary cirrhosis. In cases where frozen sections results are available at the time of transplantation, the decision to proceed with total hepatectomy and LT should be based on the presence of tumor involvement. In institutions with the capacity to perform frozen sections at all times, a laparoscopic hilar lymphadenectomy could be initially performed, with subsequent conversion to an open surgery, if the sampled LN contain no tumor. A back-up recipient, preferably with no evident tumor in order to minimize preservation time, would be transplanted in those cases where the primary recipient has positive LN. In Institutions where a pathologist is not continuously on duty (in our institution, e.g. a pathologist is only available from 08:00 to 18:00 on Monday to Friday), the removed LN could serve to better define patients at risk for early recurrence, and correspondingly inform, follow-up and eventually provide oncologic therapy. The question which remains open is what to do, if enlarged LN are present in the context of coexisting hepatitis C or secondary biliary cirrhosis and in the case that no pathologist is available. In this task, the experience of the transplant surgeon is mandatory for the decision making, although exclusion of the HCC patient from the LT without pathologic documentation is challenging.

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