Am J Transl Res 2022;14(2):990-1000
www.ajtr.org /ISSN:1943-8141/AJTR0138033

Original Article

Orthotopic liver transplantation improves postoperative quality of life, survival rate and reduces recurrence rate in patients with liver cancer

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Received August 5, 2021; Accepted December 10, 2021; Epub February 15, 2022; Published February 28, 2022

Abstract: Objective: To evaluate the impact of orthotopic liver transplantation (OLT) on postoperative quality of life (QoL), survival rate and recurrence rate of patients with liver cancer (LC). Methods: One hundred and twenty-seven patients with LC treated in our hospital from December 2016 to January 2018 were divided into two groups according to different treatment schemes. Patients in the research group (n=67) were given OLT and those in the control group (n=60 cases) were given hepatectomy. The incidence of postoperative complications, hospitalization expenses, the time to liver function recovery, surgical wound healing, pain resolution and hospitalization were compared between the two groups. The overall survival rate (OSR), disease-free survival rate (DFSR), and average survival time of patients were recorded and compared. The Visual Analogue Scale (VAS) score one day and three days after surgery, alpha-fetoprotein (AFP) level, and adverse emotion before and after operation were compared. QoL scores at six months after surgery, one-year recurrence and metastasis rates, and treatment satisfaction one year after surgery were also compared. The expression of Ki-67 and Topo IIαin the tumor-bearing group (n=5) was detected. Results: The research group presented markedly lower incidence of postoperative complications, and evidently shorter time to liver function recovery, surgical wound healing, pain resolution and hospitalization, while with noticeably higher hospitalization expenses. The one-year and five-year OSRs and DFSRs were noticeably higher, and the average survival time was remarkably longer in the research group as compared to the control group. Patients in the research group scored remarkably lower in VAS scores on the first and third day after surgery than patients in the control group. In comparison with the control group, the one-year recurrence and metastasis rates were evidently lower in the research group, and the scores of SF-36 were remarkably higher. The AFP level at one month after surgery was obviously lower in the research group, and the treatment satisfaction was greatly higher. Ki-67 in the tumor-bearing group was mainly located in the nucleus, and Topo IIα was mainly nucleus positive; the positive Ki-67 and Topo IIα expression rates in the tumor-bearing group was 66.7% and 69.8%, respectively. Conclusions: OLT can improve the postoperative QoL, survival rate and reduce the recurrence rate of LC patients.

Keywords: Orthotopic liver transplantation, liver cancer, quality of life, survival rate, recurrence rate

Introduction

Liver cancer (LC) is one of the most common malignancies in China, which can be categorized into primary and secondary cases [1]. Primary LC is the dominant type in China and also the most familiar tumor disease of the digestive system [2]. The etiology and mechanism of primary LC are not completely elucidated, but it is currently believed that the pathogenesis is affected by a variety of factors like environment and diet [3]. Epidemiological investigation and research data show that hepatitis virus infection, aflatoxin, alcohol, liver cirrhosis, nitrosamines and trace elements are all related to the pathogenesis of LC [4]. With nonspecific symptoms in the early stage, LC at middle or advanced stage have many clinical pre-

sentations, including liver pain, abdominal distension, poor appetite, fatigue, emaciation, progressive liver enlargement and upper abdominal mass [5]. Traditional surgery is the preferred and most effective way to treat LC [6]. However, with the progression of the disease to the advanced stage, the liver function of patients is seriously impaired, posing a serious threat to the life and health of the patients [7]. Therefore, exploring an effective and safe treatment method would significantly improve the life and health of LC patients [8].

Liver transplantation has been universally recognized as a routine and effective method for the treatment of end-stage liver disease (ESLD) and has also become a method for the treatment of primary LC [9]. Orthotopic liver transplantation (OLT) is a surgical treatment to implant a healthy liver into the patient's body by surgery to enable the liver function of those with ESLD to recover well [10]. In principle, the main indications of liver transplantation are various acute or chronic liver diseases that cannot be cured by other internal and surgical methods which may inevitably cause death in a short time (6-12 months) [11]. For patients with LC, liver transplantation is the optimal treatment, because liver transplantation can maximize the removal of tumor and sclerosis tissues of the liver to fundamentally eliminate the soil of liver cancer, while avoiding serious complications such as liver failure following hepatectomy [12]. Liver transplantation needs a much longer time than conventional surgery [13]. But with the rapid development of surgical techniques, a classic OLT can be successfully completed in only 4-6 h at the current stage [14]. Alpha-fetoprotein (AFP) mainly acts as a serum marker for the diagnosis and efficacy monitoring of primary LC in clinical practice [15]. Due to the trauma of the operation itself and the physical and mental injury caused by cancer to patients in varying degrees, patients need long-term follow-up and postoperative care after liver transplantation, so as to ensure their normal quality of life (QoL) [16]. However, currently, there is not enough research and working evidence regarding application of OLT in LC patients clinically [17].

It has previously been shown that, both Ki-67 and Topo IIα are important indicators involved in cell proliferation. Ki-67 is a nuclear antigen, which is specifically related to cell proliferation and can reflect the active degree of cell proliferation. Studies at home and abroad have found that it is relevant to the infiltration, proliferation, metastatic potential and prognosis of a variety of tumors and can be used as a tumor marker for predicting prognosis. DNA topoisomerase II (Topo II) is recognized as the target of many chemotherapeutics, and the current research is mostly focused on Topo IIα. Topo IIα participates in eukaryotic DNA transcription, translation, replication and chromosome separation processes, can promote tumor cell DNA synthesis, and improve tumor proliferation [12]. Studies have shown that Topo IIα is related to the prognosis of a variety of tumors. Although many studies have confirmed that Ki-67 and Topo IIα play predictive role in the prognosis of patients with multiple tumors (including liver cancer), few research has been conducted on whether the co-expression of Ki-67 and Topo IIα is related to the prognosis of liver transplantation patients with hepatocellular carcinoma. Herewith, we retrospectively analyzed the influence of OLT on postoperative QoL, survival rate and recurrence rate of LC patients to fill in this gap, and explored the relationship between the expression of Ki-67 and Topo IIα in liver cancer tissues and the prognosis of liver transplantation.

Materials and methods

General data

Sixty-seven patients with LC who received OLT treatment in our hospital from 2016 to January 2018 were analyzed retrospectively. They were included in the research group, and another 60 who underwent hepatectomy in our hospital in the same period were collected as the control group. In the research group, there were 45 males and 22 females, with an average age of (62.86±3.21) years old (35-68). The control group consisted of 44 males and 16 females, with an average age of (63.03±3.16) years old (38-72). The internal Ethics Committee approved the study protocol, and all the enrolled patients and their families were informed of the study and provided the written informed consent (Ethics code: L2020084A).

Inclusion and exclusion criteria

Inclusion criteria: (1) Patients who were in accordance with the diagnostic criteria of LC [18]; (2) Patients with first surgical treatment;

(3) Patients without metastasis. (4) Patients with indications for OLT; (5) Patients diagnosed and treated in our hospital, but not transferred patients.

Exclusion criteria: (1) Patients with severe cardiac and renal insufficiency; (2) Patients with coagulopathy; (3) Patients with contraindications to surgical anesthesia; (4) Patients with cognitive dysfunction, central nervous system and severe peripheral nerve diseases; (5) Patients with incomplete data and dropouts.(6) Patients with age <18 years old; (7) Patients with other tumors; (8) Patients with Pregnancy.

Surgical methods

Patients in the control group were treated with surgical resection. The patient was placed in a supine position. After general anesthesia through endotracheal intubation, the appropriate incision position was selected according to the position and size of the lesion. Hemostasis and drainage tube placement were performed after resection, and the incision was sutured layer by layer. During the operation, attention was paid to avoid great vessels and important tissues.

The research group was treated with classical OLT. The donor livers were all from healthy brain-dead people, and the blood type of the donors was the same with the recipients. First, the healthy liver was obtained from the donor. The patient was placed in a supine position and the diseased liver was excised after general anesthesia via endotracheal intubation, and then the donor liver was implanted into the patient. Intraoperative venous diversion was not applied in all the operations, and end-to-end anastomosis was performed in all the common bile duct, without T tube drainage. A triple immunosuppressive regimen of tacrolimus + Cellcept + glucocorticoid was used at the early stage after surgery, and tacrolimus alone was used for maintenance after 3 months.

Immunohistochemical staining

Paraffin sections are deparaffinized, hydrated, rinsed with PBS for 3×3 min, and high temperature and high pressure antigen retrieval was performed; then, 3% hydrogen peroxide solution was added and incubated at room temperature for 10 min to block endogenous peroxidase; next, after the sections were rinsed with PBS for 3×3 min, primary antibody was added and incubated for 60 min at room temperature; subsequently, it was rinsed with PBS for 3×5 min, and polymer enhancer (reagent A) was added and incubated for 20 min at room temperature; then, rinsed with PBS for 3×3 min, enzyme-labeled anti-mouse polymer (reagent B) was added and incubated for 30 min at room temperature; afterwards, it was rinsed with PBS for 3×3 min, and newly prepared DAB chromogenic solution was added. Then, the tissues were observed under the microscope. The positive color is brown-yellow. Then, it was rinsed with tap water, redyed with hematoxylin, and differentiated with 0.1% hydrochloric acid; And afterwards washed with tap water, rinsed with PBS and return to blue. Gradient alcohol dehydration and drying, and neutral resin sealing were performed.

Judgment of staining results

Two pathologists independently read the film. Ki-67 positive cells are brown particles in the nucleus. Topo IIα staining is mainly located in the nucleus, with a clear brownish-yellow or yellowish diffuse distribution. The uniformly stained area is selected, and the percentage of positive cells and the intensity of staining were counted. Semi-quantitative scoring was performed by Q-score based on intensity and heterogeneity. According to the staining intensity, 0 points (negative), 1 point (weak), 2 points (moderate), and 3 points (strong) are assigned. For heterogeneity, 0 points (0%), 1 point (1% to 25%), 2 points (26% to 50%), 3 points (51% to 75%) or 4 points (76%-100%) are assigned based on the percentage of positively stained tumor cells. The Q-score of each sample is a combination of intensity and heterogeneity, ranging from 0 to 7 points; Q-score ≥2 is positive expression, Q-score <2 is negative expression.

AFP determination

AFP levels of two groups before and 1 month after surgery were detected using Enzyme-linked immunosorbent assay (ELISA) strictly follow the instructions of the kit (Shanghai Jingkang Bioengineering Co., Ltd., Shanghai, China, JKSW-E11600).

Outcome measures

Primary outcome measures: (1) Overall survival rate (OSR), disease-free survival rate (DFSR)

and average survival time of the two groups were compared. (2) The recurrence and metastasis rates one year after surgery were compared between the two groups. (3) The tumor-bearing survival cases within three years after operation were selected as the tumor-bearing group (n=5) (3 cases were from OLT group and 2 cases were from control group).

Secondary outcome measures: (1) Incidence of postoperative complications, including wound infection, fever, pulmonary infection, abdominal hemorrhage and liver failure, were observed and recorded. (2) Surgical outcome indicators, which included hospitalization expenses and the time of liver function recovery, surgical wound healing, pain resolution and hospitalization were compared. (3) Visual analogue scale (VAS) [19] was employed for pain assessment of patients in the two groups at 1 day and 3 days after surgery, with 0 being painless, less than 3 points being mild pain that can be tolerated, 4-6 being pain that affects sleep but can be tolerated, and 7-10 being gradually intense pain that affects sleep. The lower the score, the milder the pain symptoms. (4) The assessment of each patient's anxiety and depression pre- and post-operation employed the Self-rating Anxiety/Depression Scale (SAS/SDS) [21]. Each on a 100-point scale, 50-70 points indicated mild anxiety/depression, 71-90 points indicated moderate anxiety/depression, and >90 points indicated severe anxiety/depression. The higher the score, the more severe the anxiety/depression. (5) The treatment satisfaction questionnaire made by our hospital was utilized to evaluate the treatment satisfaction of two groups after surgery. A total of 20 questions (5 points each) were scored by patients according to the treatment content of our hospital, with the total score of <70 being dissatisfied, 70-89 being satisfied, and ≥90 being very satisfied. Satisfaction = (very satisfied cases + satisfied cases)/total cases ×100%. (6) Quality of life score: The quality of life scores of the two groups were compared half a year after operation, and the SF-36 quality of life scale was used to evaluate the quality of life of both groups 6 months after operation. The quality of life of the patients was evaluated with reference to the SF-36 scale developed by the American Institute of Medical Research, which included eight items: general health, physical functioning, role-physical, bodily pain, vitality, social functioning, role-emotional and mental health. The higher the score, the better the quality of life is.

Statistical methods

Data were statistically analyzed and visualized by SPSS24.0 (IBM Corp, Armonk, NY, USA) and GraphPad Prism 7, respectively. Counting data was expressed by [n (%)] and analyzed by Chi-square test; Measurement data were expressed as (x±sd), and the differences were analyzed by the independent samples T test between groups, and paired T test within the same group before and after surgery. P<0.05 suggested a significant difference.

Results

General information

The general clinical baseline data such as gender, age, BMI, Child-Pugh classification, number of lesions, marriage, place of residence, educational background, smoking history and drinking history were similar between the two groups (P>0.05) (**Table 1**).

Incidence of postoperative complications

The incidence of postoperative complications was notably lower in the research group as compared to the control group (5.97% vs 26.67%; P<0.05) (**Table 2**).

Surgical outcome indexes

The research group exhibited notably shorter time to liver function recovery, surgical wound healing, pain resolution and hospitalization than the control group after surgery, with noticeably higher hospitalization expenses (P<0.05) (**Table 3**).

OSR, DFSR and average survival time

In comparison with the control group, the 1-year and 5-year OSRs and DFSRs were observably higher and the average survival time was noticeably longer in the research group (P<0.05) (**Table 4**).

Rates of recurrence and metastasis

The one-year recurrence and metastasis rates of patients in the research group were 11.94%

Table 1. Comparison of general information between the two groups ([n (%)], x±sd)

Classification	Research group (n=67)	Control group (n=60)	t/χ^2 value	*P* value
Gender			0.574	0.448
Male	45 (67.16)	44 (73.33)		
Female	22 (32.84)	16 (26.67)		
Age (years old)	62.86±3.21	63.03±3.16	0.300	0.764
BMI (kg/m^2)	21.46±3.14	21.12±3.05	0.617	0.538
Child-Pugh classification			1.568	0.456
Phase A	3 (4.48)	5 (8.33)		
Phase B	40 (59.70)	30 (50.00)		
Phase C	24 (35.82)	25 (41.67)		
Number of lesions			0.219	0.639
Single	42 (62.69)	40 (66.67)		
Multiple	25 (37.31)	20 (33.33)		
Marital status			0.107	0.742
Married	41 (61.19)	35 (58.33)		
Single or widowed	26 (38.81)	25 (41.67)		
Place of residence			0.015	0.901
Urban	32 (47.76)	28 (46.67)		
Rural	35 (52.24)	32 (53.33)		
Educational background			0.373	0.541
≥ High school	20 (29.85)	15 (25.00)		
< High school	47 (70.15)	45 (75.00)		
History of smoking			0.027	0.868
Yes	50 (74.63)	44 (73.33)		
No	17 (25.37)	16 (26.67)		
History of drinking			0.009	0.923
Yes	43 (64.18)	39 (65.00)		
No	24 (35.82)	21 (35.00)		

and 7.46%, which were evidently lower than those in the control group (30.00% and 26.67%) (P<0.05) (**Table 5**).

VAS scores

Patients in the research group scored statistically lower in VAS than patients in the control group on the 1st and 3rd day after surgical treatment (P<0.001) (**Figure 1**).

SF-36 scores

The SF-36 score of the research group was higher than that of the control group 6 months after operation (P<0.001) (**Figure 2**).

SAS and SDS scores

SAS and SDS scores differed insignificantly between the two groups before surgery (P>0.05), while both dropped markedly in the two groups after surgical treatment, with lower scores in the research group (P<0.001) (**Figure 3**).

AFP level

AFP levels were not statistically different between two groups before surgery (P>0.05) but declined notably in both the control group and the research group one month after surgery, with lower values in the research group (P<0.001) (**Figure 4**).

Treatment satisfaction

After treatment, the treatment satisfaction of the research group was 94.03%, which was notably lower than 76.67% of the control group (P<0.05) (**Table 6**).

Expression of Ki-67 and Topo IIα in tumor-bearing group

Ki-67 in the tumor-bearing group was mainly located in the nucleus, Topo IIα was mainly nucleus positive, the positive expression of Ki-67 and Topo IIα in the tumor-bearing group was 66.7% and 69.8%, respectively (**Figure 5**).

Discussion

LC is one of the malignancies with high incidence, and the mortality is at the forefront of the digestive system [22]. Since early LC has no obvious clinical symptoms, most of the patients were diagnosed at the middle and advanced stages [23]. At present, there is no special radical treatment for advanced LC, and conventional tumor treatment methods such as interventional therapy, radiofrequency therapy and systemic chemotherapy were mostly used clinically [24]. However, none of these treatments can well control tumor recurrence and metastasis, nor can they ameliorate the survival rate and QoL of patients [25]. Liver transplantation, as an effective treatment for ESLD, has been extensively applied and accepted in LC treatment with the development of modern medicine and technology [26].

Table 2. Comparison of the incidence of postoperative complications between the two groups [n (%)]

Groups	Wound infection	Fever	Pulmonary infection	Abdominal bleeding	Hepatic failure	Total incidence
Research group (n=67)	2 (2.99)	1 (1.49)	1 (1.49)	0 (0.00)	0 (0.00)	4 (5.97)
Control group (n=60)	4 (6.67)	4 (6.67)	3 (5.00)	2 (3.33)	3 (5.00)	16 (26.67)
χ^2	-	-	-	-	-	10.220
P	-	-	-	-	-	0.0014

Table 3. Comparison of surgical outcome indexes between the two groups (x±sd)

Groups	Time of liver function recovery (d)	Time of surgical wound healing (d)	Time of pain resolution (d)	Hospitalization time (d)	Hospitalization expenses (10,000 yuan)
Research group (n=67)	5.32±1.14	8.06±2.27	3.82±2.41	9.41±1.37	36.49±10.32
Control group (n=60)	11.28±2.15	13.13±2.65	6.17±2.34	16.87±1.89	5.46±1.08
t	19.800	11.610	5.562	25.650	23.170
P	<0.001	<0.001	<0.001	<0.001	<0.001

Table 4. Comparison of overall survival rate, disease-free survival rate and average survival time between the two groups [n (%)]

Groups	One-year overall survival rate	3-year overall survival rate	One-year disease-free survival rate	3-year disease-free survival rate	Average survival time (years)
Research group (n=67)	57 (85.07)	39 (58.21)	60 (89.55)	34 (50.75)	3.27±0.86
Control group (n=60)	36 (60.00)	22 (36.67)	39 (65.00)	18 (30.00)	2.54±0.93
t/χ^2	10.150	5.885	11.100	5.634	4.595
P	0.0014	0.0153	<0.001	0.0176	<0.001

Table 5. Comparison of recurrence and metastasis rates between the two groups [n (%)]

Groups	Recurrent rate	Metastasis rate
Research group (n=67)	8 (11.94)	5 (7.46)
Control group (n=60)	18 (30.00)	16 (26.67)
χ^2	6.341	8.458
P	0.0118	0.0036

Whereas, there are relatively few studies on the influence of OLT on the survival rate, recurrence rate and QoL of patients. Accordingly, this study retrospectively analyzed the surgical effect of OLT, so as to provide useful reference for clinical practice.

Liu JB et al. [27] found that for LC patients with preserved liver function, the OSR and QoL of LC patients who received OLT were significantly higher than those who received resection. We showed that compared with the control group, the one-year and five-year OSRs and DFSRs were notably higher and the average survival time was statistically longer in the research group, indicating that patients undergoing OLT

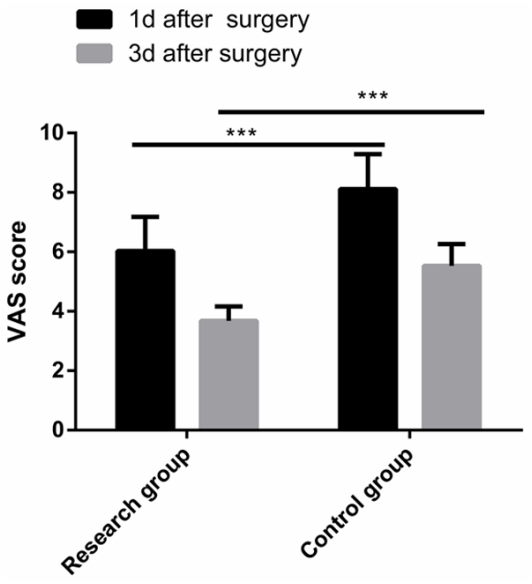

Figure 1. Comparison of VAS scores. VAS scores of patients in the research group were significantly lower than those in the control group on the 1st and 3rd day after operation. Note: ***P<0.001.

can effectively improve the OSR, DFSR and prolong the average survival time, which is similar

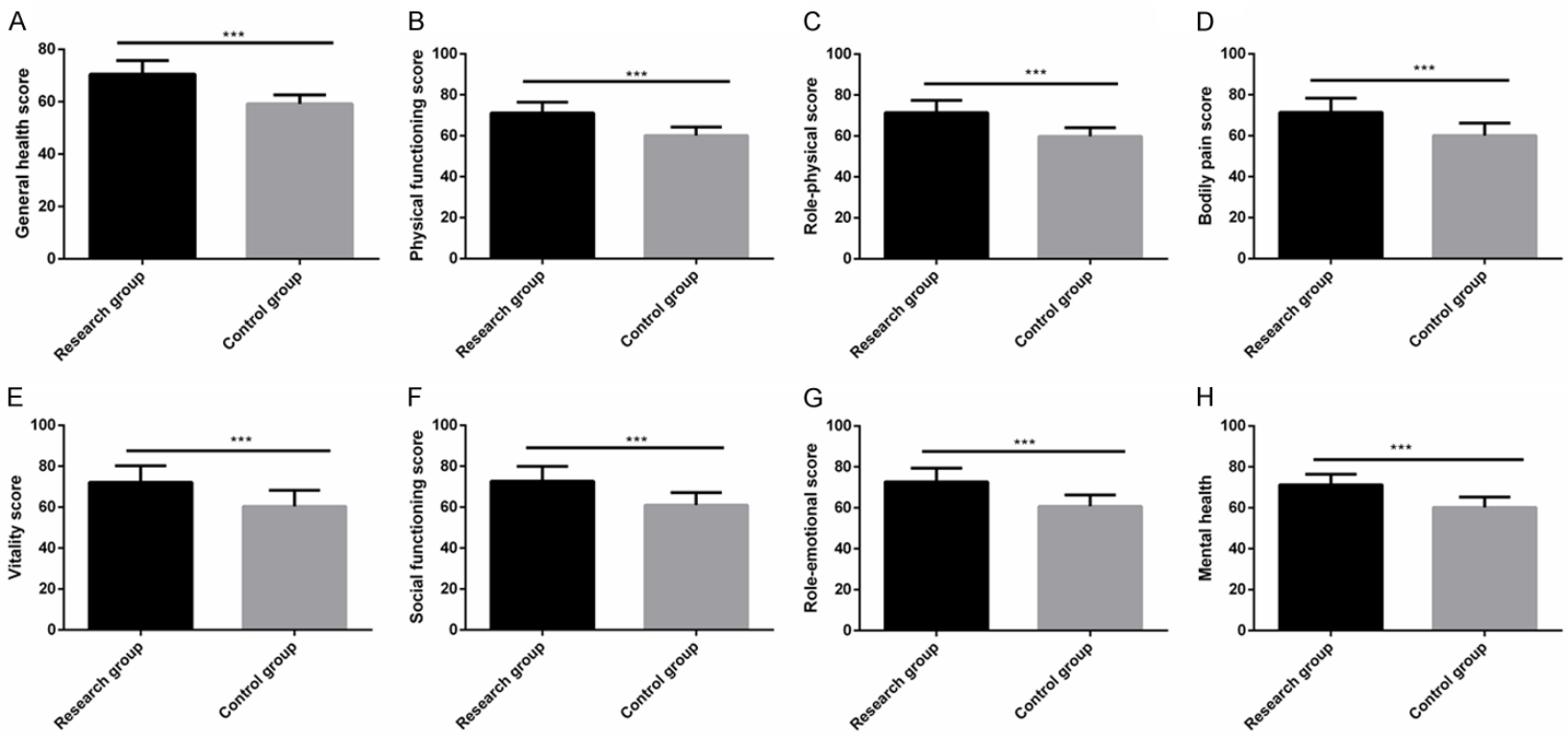

Figure 2. Comparison of SF-36 scores. Six months after operation, the scores of general health (A), physical functioning (B), role-physical (C), bodily pain (D), vitality (E), social functioning (F), role-emotional (G) and mental health (H) of patients in the research group were significantly higher than those in the control group. Note: ***P<0.001.

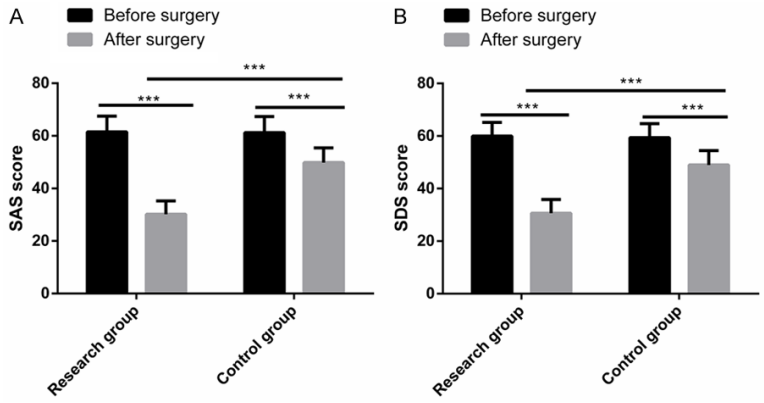

Figure 3. Comparison of SAS and SDS scores. After surgical treatment, SAS scores (A) and SDS scores (B) of patients in the two groups decreased significantly, and the scores in the research group were significantly lower than those in the control group. Note: ***P<0.001.

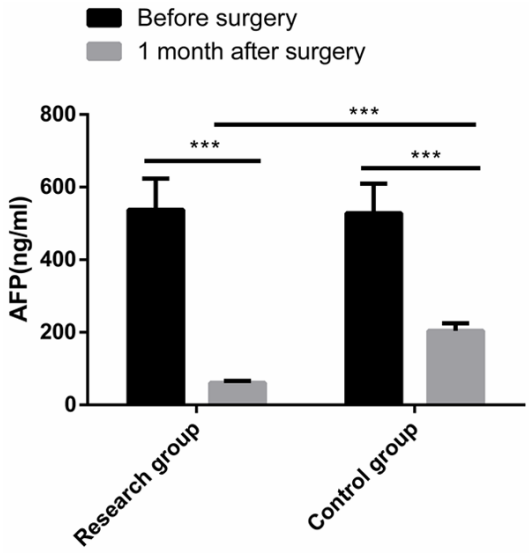

Figure 4. Comparison of AFP level. One month after surgery, the AFP level of patients in both groups decreased significantly, and the AFP level in the research group was significantly lower than that in the control group. Note: ***P<0.001.

to the research results of Liu JB. In addition, statistically lower rates of postoperative complications, recurrence and metastasis were detected in the research group, suggesting that OLT can enormously reduce postoperative complications, tumor recurrence rate and metastasis rate. Similarly, Benjamin AJ et al. [28] reported that OLT has survival advantages over margin-negative resection for patients with small unifocal hepatocellular carcinoma and liver function preservation, which can reduce postoperative complications and recurrence rate. T et al. [29] found that OLT for LC patients could validly promote the recovery of liver function, reduce the hospitalization time and improve the OSR of patients. In this research, we observed noticeably less time for liver function recovery, surgical wound healing, pain resolution and hospitalization but remarkably higher hospitalization expenses in the research group, indicating that OLT can facilitate the recovery of liver function and postoperative rehabilitation of patients, albeit with much higher cost compared with resection, which is similar to the research results of Chan T. Furthermore, we found that the VAS scores were noticeably lower in the research group than in the control group on the 1st and 3rd day after surgery, indicating that LC patients undergoing OLT can reduce the perioperative pain. We also evaluated the patients' QoL and SAS and SDS scores at 6 months postoperatively. The SF-36 score was statistically higher and the SAS and SDS scores were obviously lower in the research group compared with the control group, indicating that OLT can improve patients' QoL and mitigate their negative emotion after surgery. Jover-Aguilar M et al. [30] revealed profoundly improved short-term and medium-term QoL of patients undergoing OLT in their study, which were similar to our research results. AFP is a powerful indicator to monitor LC progression, so we studied and compared the serum AFP levels of patients one month after surgery. The AFP level in the research group was markedly lower than that in the control group, which indicates patients receiving OLT had better tumor control after surgery. Feng J et al. [31] discovered that the AFP level of LC patients undergoing OLT decreased more, and it can be used as an independent predictor of postoperative recurrence, which agrees with our findings. Finally, we investigated the treatment satisfaction of patients, and found that the treatment satisfaction of the research group was remarkably higher, indicating that patients are more willing to receive OLT if the economic conditions

Table 6. Comparison of treatment satisfaction between the two groups [n (%)]

Classification	Research group (n=67)	Control group (n=60)	χ^2 value	*P* value
Very satisfied	49 (73.13)	19 (31.67)	-	-
Satisfied	14 (20.90)	27 (45.00)	-	-
Dissatisfied	4 (5.97)	14 (23.33)	-	-
Satisfaction	63 (94.03)	46 (76.67)	7.845	0.0051

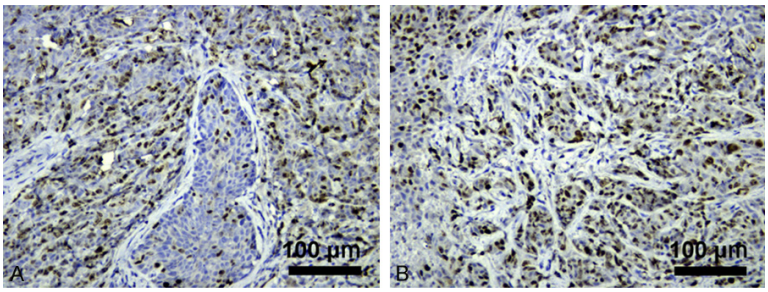

Figure 5. Expression of Ki-67 and Topo IIα in tumor-bearing group. A. Expression of Ki-67; B. Expression of Topo IIα (50 μm) (3 cases were from OLT group and 2 cases were from control group).

allows. This study shows that Ki-67 and TOPO IIα are related to the overall survival rate of liver cancer patients after liver transplantation. It suggested that Ki-67 and TOPO IIα can be used as indexes to predict the clinical prognosis of patients after liver transplantation.

However, there are still some shortcomings. For example, we can carry out animal experiments to better explain the advantages of OLT from the perspective of mechanism. Besides, the prognostic risk factors can be analyzed during the long-term follow-up of patients to provide clinical treatment plans. In the future, we will carry out research from the above perspectives

To sum up, the implementation of OLT for patients with advanced LC can validly improve the OSR and DFSR, prolong the survival time, reduce postoperative complications, recurrence rate and metastasis rate, and facilitate the recovery of postoperative liver function and postoperative rehabilitation; moreover, it can alleviate the pain of patients, relieve the adverse emotion after surgery, and improve the postoperative QoL and treatment satisfaction of patients, albeit with higher hospitalization expenses.

Acknowledgements

This study is financially supported by National Natural Science Foundation of China (81572452).

Disclosure of conflict of interest

None.

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