

MANAGEMENT OF PULMONARY NODULES IN PATIENTS UNDERGOING LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA

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Abstract

The lungs are among the most common sites of recurrence in patients undergoing liver transplantation (LT) for hepatocellular carcinoma (HCC). The optimal management of pulmonary nodules in this patient group remains controversial. We retrospectively evaluated twelve patients who underwent liver transplantation for HCC and subsequently had surgical resection of pulmonary nodules. Demographic characteristics, tumor features, surgical techniques (video-assisted thoracoscopic surgery (VATS) or thoracotomy), immunosuppression protocols, and survival data were analyzed using the Kaplan-Meier method. Overall survival rates at 1, 3, and 5 years were 83%, 42%, and 17%, respectively. One patient underwent five separate pulmonary metastasectomy procedures and survived for 82 months. Pathological examination revealed a second primary lung cancer (two squamous cell carcinomas, one adenocarcinoma, and one sarcomatoid carcinoma) in four patients (33%) and benign lesions (organizing pneumonia and Pneumocystis carinii infection) in two patients (17%). VATS was performed in 67% of patients. Among patients with HCC metastasis, those converted to mTOR inhibitor-based immunosuppression had longer survival than those maintained on calcineurin inhibitors. The median survival was 23.5 months. Surgical resection of pulmonary nodules provides a significant survival benefit in selected patients. Minimally invasive techniques markedly reduce morbidity. However, given the high incidence of second primary lung cancer, histopathological confirmation is strongly recommended rather than assuming all pulmonary nodules are HCC metastases. The immunosuppression regimen appears to influence outcomes in HCC recurrence.

Keywords: Hepatocellular carcinoma, Liver transplantation, Lung neoplasms, Pulmonary metastasectomy, Second primary neoplasms.

INTRODUCTION

Hepatocellular carcinoma (HCC) remains one of the leading causes of cancer-related deaths worldwide. For patients with advanced cirrhosis or HCC meeting Milan criteria, liver transplantation offers an ideal treatment modality by simultaneously addressing both the underlying liver disease and the malignancy (Filgueira, 2019; Parraga et al., 2025). HCC recurrence after transplantation presents a significant clinical challenge, occurring in approximately 8-20% of patients, particularly within the first two years. Among patients who develop recurrence, the lungs account for 40-60% of all extrahepatic metastases, making them the most common metastatic site (Comacchio, Melan, Zmabello, Mammana & Rea, 2022).

The optimal treatment approach for lung metastases after liver transplantation remains controversial. Various options exist, including systemic therapies, local ablation methods, and modification of immunosuppression. Surgical removal has yielded positive results in certain patient groups. Recent work in 2024 suggests that immunosuppressive agents may modulate the pulmonary microenvironment, with mTOR inhibitors potentially exhibiting more protective effects compared to calcineurin inhibitors (Chen et al., 2024). Patients who undergo solid organ transplantation face a 2-4 times higher risk of developing malignancies compared to the general population (Engels et al., 2011). Studies have also shown that inflammatory conditions after transplantation, such as pneumonia, may facilitate lung metastasis development (Ma et al., 2022; Zhuang et al., 2024).

While pulmonary metastasectomy is not a new concept, our series uncovers several findings that challenge the current clinical routine. We report an exceptionally high rate (33%) of second primary lung cancers among pulmonary nodules, significantly exceeding most published series. This challenges the common assumption that post-transplant pulmonary lesions represent HCC recurrence. We also present the long-term outcome of a patient who underwent five sequential pulmonary resections, whose survival exceeded 82 months, demonstrating the feasibility of aggressive repeat metastasectomy in carefully selected cases. Finally, we present contemporary data on the predominant use of minimally invasive techniques (video-assisted thoracoscopic surgery [VATS]) in this immunosuppressed population and analyze immunosuppression protocols and their impact on outcomes.

This study aims to evaluate the role of surgical resection of pulmonary nodules and the impact of this procedure on survival in patients who have undergone liver transplantation for HCC. We also sought to determine the incidence and clinical significance of second primary lung cancers and to analyze prognostic factors, including immunosuppressive regimens.

This study also makes an original contribution to the literature in three respects: the observed high incidence of second primary lung cancer, the potential for long-term survival following repeat metastasectomy in selected cases, and the combined evaluation of the potential effects of immunosuppressive regimens and minimally invasive surgery on outcomes.

MATERIAL AND METHOD

We conducted a retrospective cohort study of all patients who underwent liver transplantation for HCC at İnönü University Hospital between January 2010 and December 2023 and who subsequently developed pulmonary nodules that required surgical resection. The İnönü University Ethics Committee approved this study protocol (Ethics Committee No: 2025/7394).

The inclusion criteria are as follows:

- Confirmation of an HCC diagnosis in the pathology report of the resected tissue
- Detection of lung nodules on post-transplant chest computed tomography (CT) (Figure 1).
- Lung lesions surgically removed at our institution

- Availability of complete clinical, pathological, and follow-up data

Exclusion criteria are as follows:

- Presence of known lung nodules prior to liver transplantation
- Treatment of lung lesions using non-surgical methods
- Insufficient follow-up data (<3 months post-resection)

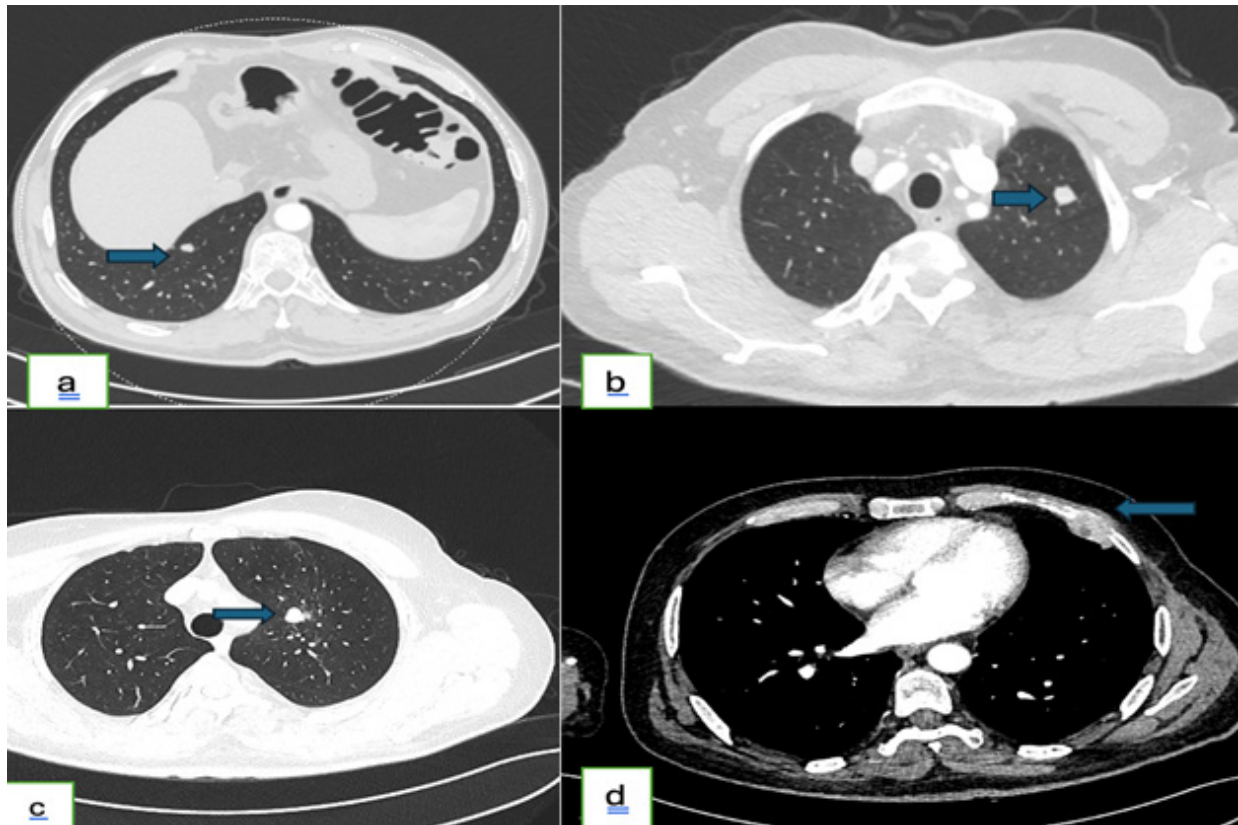


Figure 1. Axial computed tomography image showing a pulmonary nodule (white arrow) in the left upper lobe detected during post-transplant surveillance.

We systematically extracted data from electronic medical records, surgical databases, and pathology reports. Pre-transplant variables included patient demographics (age, sex), etiology of liver disease, liver function scores (MELD, Child-Pugh classification), alpha-fetoprotein (AFP) levels, tumor characteristics on pre-transplant imaging (number of lesions, maximum tumor diameter, presence of vascular invasion), and Milan criteria status. Post-transplant variables included initial and maintenance immunosuppression regimen (calcineurin inhibitor-based vs. mTOR inhibitor-based), time from transplantation to pulmonary nodule detection, pulmonary nodule characteristics (location, number, size), surgical approach (VATS vs. thoracotomy), extent of resection (wedge resection, segmentectomy, lobectomy), perioperative complications, final pathological diagnosis, and survival outcomes. These variables were selected based on their known or potential effects on tumor recurrence, disease progression, and overall survival in patients who have undergone liver transplantation and have hepatocellular carcinoma.

Patients were divided into three groups based on final pathology: those with confirmed HCC metastases, those with second primary lung cancers, and those with benign lesions. We analyzed the HCC metastasis group in greater detail, examining how pre-transplant tumor features, immunosuppression regimens, timing of pulmonary recurrence, lesion patterns, surgical technique, and survival outcomes compared across patients.

All liver transplant recipients underwent routine chest imaging (chest radiograph every 6 months and CT annually), per institutional protocol. Additional imaging was performed based on symptoms or elevated tumor markers. A multidisciplinary board evaluated pulmonary nodules detected on imaging. Surgical resection was recommended for patients with adequate cardiopulmonary reserve, resectable disease, controlled or absent hepatic recurrence, and no evidence of extrathoracic metastases.

Overall survival (OS) was defined as the time from first pulmonary resection to death from any cause or to last follow-up. We generated Kaplan-Meier survival curves and compared survival between subgroups (Milan criteria status, pathological diagnosis, immunosuppression regimen type) using the log-rank test. Continuous variables are presented as median (range) and categorical variables as frequencies and percentages. All statistical analyses were performed using SPSS version 25.0. We considered p -values <0.05 statistically significant. Because the sample size is relatively small, the results should be interpreted with caution, and the generalizability of the findings may be limited.

RESULTS

Our study cohort comprised twelve patients (nine males and three females) who underwent liver transplantation for HCC and later required pulmonary resection. One patient was aged 21-40 years, seven were aged 41-60 years, and four were aged 61-80 years. The etiologies of underlying liver disease were hepatitis B virus ($n=5$, 42%), hepatitis C virus ($n=4$, 33%), alcoholic cirrhosis ($n=2$, 17%), and cryptogenic cirrhosis ($n=1$, 8%). Eight patients (67%) met the Milan criteria before transplantation, while four (33%) exceeded the criteria. The median pre-transplant AFP level was 47 ng/mL (range: 4-892 ng/mL). The mean pre-transplant AFP level was 47 ng/mL (range: 4-892 ng/mL). The mean time from liver transplantation to the detection of a lung nodule was 30 months (range: 1-121 months) (Table 1).

Table 1. Demographic and Clinical Characteristics of Patients Undergoing Pulmonary Resection After Liver Transplantation

Variable	Subgroup	n (%)
Gender	Male	9 (75)
	Female	3 (25)
Age Distribution	21-40 years	1 (8)
	41-60 years	7 (58)
	61-80 years	4 (33)
Localization	Right upper lobe	3 (25)
	Left upper lobe	6 (50)
	Left lower lobe	2 (17)
	Bilateral	1 (8)
Number of Metastases	Single	8 (67)
	2-3	3 (25)
	Multiple (5x operated)	1 (8)
Metastasis Size	<1 cm	1 (8)
	1-3 cm	2 (17)
	3-6 cm	7 (58)
	>6 cm	2 (17)
Pathology	HCC Metastasis	6 (50)
	Primary Lung Cancer (Squamous)	2 (17)
	Primary Lung Cancer (Adeno)	1 (8)
	Primary Lung Cancer (Sarcomatoid)	1 (8)
	Benign (Organizing Pneumonia)	1 (8)
	Benign (P. carinii)	1 (8)
Surgical Technique	VATS	8 (67)
	Thoracotomy	4 (33)
Resection Type	Wedge	8 (67)
	Lobectomy	4 (33)
Milan Criteria	Within	8 (67)
	Beyond	4 (33)
Median Survival (HCC)		23.5 mo (18-82)
Median Survival (All)		23.5 mo (2-82)
1-Year Survival		10/12 (83%)
3-Year Survival		5/12 (42%)
5-Year Survival		2/12 (17%)

Final pathological examination of resected pulmonary lesions revealed three distinct categories: HCC metastases in 6 patients (50%), second primary lung cancers in 4 patients (33%), and benign lesions in 2 patients (17%). The four cases of second primary lung cancer included two squamous cell carcinomas, one adenocarcinoma, and one sarcomatoid carcinoma. The two benign lesions were organizing pneumonia and *Pneumocystis carinii* infection. One month after transplantation, a patient who developed a lung nodule was diagnosed with organizing pneumonia; the second benign case (*Pneumocystis* infection at 8 months) occurred in a patient receiving enhanced immunosuppressive therapy due to acute cellular rejection.

Among the six patients with confirmed HCC lung metastases, four (67%) were within the Milan criteria at transplantation, while two (33%) exceeded the Milan criteria. The median time to pulmonary recurrence was 36 months (range: 12-121 months), with early recurrence (<24 months) in 2 patients and late recurrence (≥ 24 months) in 4 patients. AFP levels were elevated at the time of detection of pulmonary recurrence in 4 patients (median, 156 ng/mL). All patients initially received tacrolimus-based immunosuppression. However, at the time pulmonary recurrence was detected, 4 patients (67%) remained on calcineurin inhibitor-based regimens (tacrolimus), while 2 patients (33%) had been converted to mTOR inhibitor-based regimens (everolimus) more than 12 months prior to recurrence, a change initially made because of declining renal function. Four patients presented with solitary pulmonary lesions (67%), while two had multiple lesions (2–4 each). VATS was performed in 4 patients (67%) and thoracotomy in 2 patients (33%). Median survival from first pulmonary resection was 23.5 months (range: 8-82 months) in this subgroup (Table 2).

Table 2. Individual Patient Characteristics and Outcomes

Case	Age	Gender	Milan	Time to Met (mo)	Number	Location	Procedure	Pathology	Survival	Status
1	58	M	Within	17	Single	LUL	Wedge	HCC Met	18 mo	Deceased
2	71	M	Within	30	Single	LUL	Lobectomy	Squamous Ca	62 mo	Alive
3	47	M	Within	31	Single	LLL	Wedge	HCC Met	19 mo	Deceased
4	48	M	Within	65	2-3	RUL	Wedge	Adeno Ca	2 mo	Deceased
5	34	F	Beyond	30	2-3	LUL	Lobectomy	HCC Met	21 mo	Deceased
6	62	M	Beyond	31	Single	LLL	Wedge	HCC Met	26 mo	Deceased
7	56	M	Within	1	Multiple	Bilateral	5x Wedge	HCC Met	82 mo	Alive
8	61	M	Within	30	Single	LUL	Wedge	Organizing Pneum	23 mo	Deceased
9	70	F	Beyond	121	Single	LUL	Lobectomy	HCC Met	23 mo	Deceased
10	64	F	Beyond	7	2-3	RUL	Wedge	P. carinii	21 mo	Alive
11	57	M	Within	56	Single	RUL	Wedge	Sarcomatoid Ca	19 mo	Deceased
12	58	M	Within	22	Single	RUL	Lobectomy	Squamous Ca	37 mo	Alive

Comparison of outcomes within the HCC metastasis group showed that the two patients who achieved long-term survival (>3 years) shared several characteristics. Both were within Milan criteria at transplant, experienced late recurrence (>36 months post-transplant), had solitary pulmonary lesions resected via VATS, and had been converted to mTOR inhibitor immunosuppression (everolimus) before recurrence detection.

One patient underwent a single resection and remains alive at 48 months. The other (Case 7) underwent five sequential resections over 68 months and remains alive 82 months after the first pulmonary resection.

Case 7 is particularly instructive in terms of its clinical course. The patient met the Milan criteria at the time of transplantation. Because of chronic kidney disease, the immunosuppressive regimen was switched to everolimus 18 months after transplantation.

The first lung recurrence, a single 1.5-cm nodule in the right lower lobe, was detected at 24 months resected via VATS. Subsequent recurrences were detected intermittently and treated surgically. Details of the recurrences are summarized in Table 3.

Table 3. Lung and chest wall recurrences and treatment methods in Case 7.

Month	Localization	Treatment
24	Right lower lobe	VATS resection
30	Left upper lobe	VATS resection
42	Right upper lobe	VATS resection
56	left lower lobe	VATS resection
68	Chest wall	Thoracotomy

The four patients diagnosed with second primary lung cancers presented at a median of 52 months post-transplantation (range: 36-89 months), which was substantially longer than that of the HCC metastasis group. None had elevated AFP at diagnosis. All patients underwent VATS resection, with lobectomy in three patients and wedge resection in one. Median survival from lung cancer diagnosis was 19.5 months (range: 11-34 months). The patient with sarcomatoid carcinoma (stage IIB) died at 11 months from progressive disease. The others either had no recurrence at the last follow-up or died from unrelated causes.

For the entire cohort, VATS was the surgical approach in 8 patients (67%), and thoracotomy was the surgical approach in 4 patients (33%). The median hospital stay was 4 days for VATS compared with 7 days for thoracotomy.

Overall survival analysis of the entire cohort revealed 1-year, 3-year, and 5-year OS rates of 83%, 42%, and 17%, respectively, with a median OS of 23.5 months. When stratified by pathological diagnosis, the median OS was 23.5 months for patients with HCC metastasis and 19.5 months for those with second primary lung cancer; both patients with benign lesions remained alive at last follow-up. Milan criteria status at transplantation showed a trend toward better survival for patients within criteria (median OS 28 months vs. 18 months), though this did not reach statistical significance ($p=0.62$) (Figure 2).

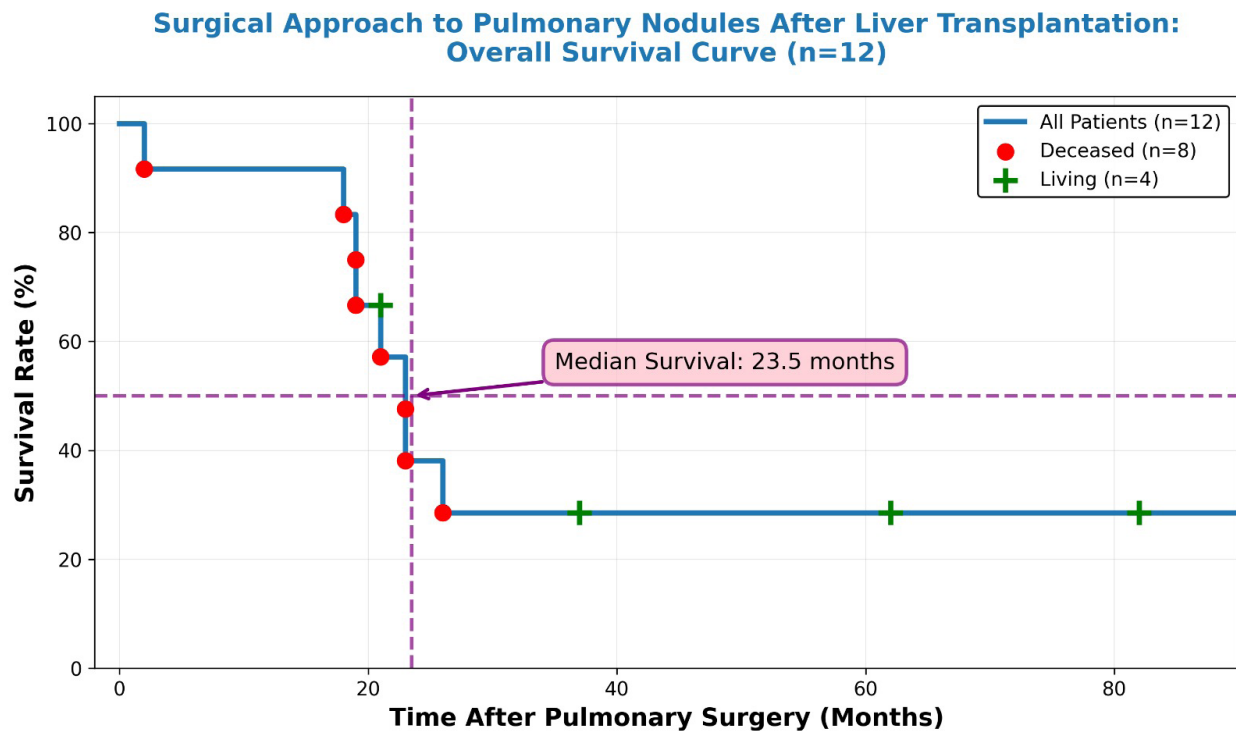


Figure 2. Kaplan-Meier survival estimation for the entire cohort (n=12). Median longevity was 23.5 months. Red circles denote deceased patients; green crosses denote patients who were alive at final contact.

DISCUSSION

One-third of pulmonary nodules in post-LT patients were identified as second primary malignancies rather than HCC recurrences. This 33% rate exceeds most published figures and has significant implications for clinical management. These findings challenge the common assumption that every new lung nodule detected in a patient who has survived HCC is a metastasis and underscore the necessity of histopathological confirmation prior to making treatment decisions. The presence of benign pathology in 17% of cases reinforces the need for tissue sampling, regardless of HCC history.

Solid-organ transplant recipients face an elevated risk of malignancy. Recent data confirmed that liver recipients develop additional cancers at two to four times the rate of the general population (Engels et al., 2011). Persistent immunosuppression, chronic viral infection, and ongoing inflammation all contribute to this risk. The 33% rate of independent lung primaries in our study ranks among the highest reported in the literature. Several factors may explain this high frequency: rigorous histopathological examination protocols at our institution, a longer median follow-up, allowing detection of late-developing primary tumors, underlying risk factors in our patient population (smoking history, viral hepatitis), and potential referral bias toward complex cases at our tertiary center. Clinically, this high rate reinforces the need for diagnostic biopsy or resection with frozen section for all post-transplant pulmonary lesions. Radiological features alone cannot reliably distinguish HCC metastases from primary lung cancers, and inappropriate management decisions based on assumptions could deprive patients of potentially curative interventions.

Maintenance immunosuppression is increasingly recognized as having a critical impact on HCC recurrence and metastatic progression. Calcineurin inhibitors (tacrolimus and cyclosporine), while effective in preventing allograft rejection, promote tumor progression by multiple mechanisms. These include facilitating epithelial-to-mesenchymal transition, upregulating VEGF expression, enhancing angiogenesis,

and suppressing antitumor immune surveillance (Chen et al., 2024; Guba, Graeb, Jauch & Geissler, 2004; Rodriguez-Peralvarez et al., 2013). In contrast, mTOR inhibitors (sirolimus, everolimus) exert antiproliferative and antiangiogenic effects. They may limit metastatic spread by inhibiting the PI3K/AKT/mTOR signaling pathway (Grigg, Sarri, Gow & Yeomans, 2019; Menon, Hakeem & Heaton, 2014).

Our data support these mechanistic observations. In the HCC metastasis subgroup, all four patients who died within 2 years were maintained on calcineurin inhibitor-based regimens. The two long-term survivors, however, had been converted to mTOR inhibitor protocols before recurrence was detected. In contrast, the four patients who died within 2 years all remained on calcineurin inhibitor-based regimens (tacrolimus) throughout their post-transplant courses, with a median survival of 14.5 months (range: 8-22 months). Although the sample size is small and these observations cannot generally be generalized, this finding is consistent with the growing body of evidence suggesting that switching to mTOR inhibitors may positively alter the biological behavior of recurrent HCC (Menon et al., 2014; Schnitzbauer et al., 2010).

Several prognostic factors emerged in our cohort. Patients with HCC metastases who survived beyond 3 years shared the following favorable characteristics: adherence to the Milan criteria at transplantation, a longer time to pulmonary recurrence (>24 months), solitary pulmonary lesions, conversion to mTOR-inhibitor immunosuppression, and complete surgical resection via VATS. Conversely, poor prognostic features included exceeding the Milan criteria, early recurrence (<12 months), multiple pulmonary lesions, and maintenance therapy with calcineurin inhibitors.

A patient who underwent five consecutive lung resections and survived for 82 months demonstrates the potential benefit of aggressive surgical management in carefully selected cases. This individual met the Milan criteria at transplantation, experienced late initial recurrence (24 months), and was converted to everolimus-based immunosuppression. Each subsequent resection addressed an oligometastatic recurrence, with complete resection achieved. This case supports the concept that repeat metastasectomy remains a viable option when surgical criteria are met (Lin et al., 2023; Pascale, Marandola, Frongillo, Nure & Agnes, 2025). The patient remains disease-free 82 months after the first lung resection. This outcome demonstrates the potential benefit of combining aggressive surgical management with mTOR inhibitor-based immunosuppression.

The median survival of patients with confirmed metastatic HCC was 23.5 months, consistent with previous studies. Chen and colleagues in 2021 reported similar median survival in 52 patients who underwent metastasectomy after transplantation (Jeong et al., 2021). An Italian multicenter study involving 25 patients reported longer average survival of 51 months (Invernizzi et al., 2020). These differences likely reflect variations in patient selection, follow-up intensity, adjuvant treatment protocols, and immunosuppression strategies. Evidence supports mTOR inhibitor-based protocols for potentially reducing tumor recurrence (Grigg et al., 2019).

Thoracoscopic approaches have gained substantial traction in recent years. In our cohort, minimally invasive techniques accounted for two-thirds of procedures, providing reduced pain, shorter hospitalization, and faster recovery (Elkhayat, Hamza, Elshoeby, Omar, & Gaber, 2022; Lee et al., 2021). The benefits of VATS are particularly relevant in immunosuppressed transplant populations, where minimizing surgical trauma and reducing perioperative complications are paramount. Our VATS patients had a median hospital stay of 4 days, compared to 7 days for thoracotomy patients; complication rates were comparable. Contemporary 2025 publications continue to report favorable surgical outcomes for post-transplant HCC recurrence (Endo, Bekki, Hernandez-Alejandro & Tomiyama, 2025). The feasibility of repeat VATS procedures in our Case 7 demonstrates that prior thoracoscopic surgery does not preclude subsequent minimally invasive interventions.

Managing recurrent HCC after transplantation requires coordinated, multidisciplinary input. Pharmacological therapy, focal ablation, and surgical excision each have situational merit depending on individual patient circumstances (Marrone et al., 2023). The study's limitations include its retrospective

design, single-center nature, and small sample size; these factors limit its statistical power and restrict its generalizability. However, the high frequency of second primaries (33%, among the highest reported), extended follow-up duration, detailed characterization of the repeat metastasectomy case, and predominant use of VATS approaches represent the primary strengths of this investigation.

CONCLUSION

Managing pulmonary nodules in patients after liver transplantation for HCC requires a multidisciplinary approach. Surgical resection may offer survival benefits, and minimally invasive techniques such as VATS reduce operative morbidity. Histopathological confirmation is mandatory for all lesions. In our patient cohort, 33% of nodules were identified as second primary lung cancers rather than as HCC metastases. Conversion to mTOR inhibitor-based immunosuppression may favorably influence outcomes after HCC recurrence. Aggressive repeat metastasectomy appears to be a viable option in selected cases with oligometastatic disease. Transplant centers should provide long-term, careful monitoring for emerging malignancies in this high-risk patient group.

Main Points

- Surgical resection of pulmonary nodules following liver transplantation for HCC provides a significant survival benefit in selected patients.
- One-third of pulmonary lesions in this population represent second primary lung cancers rather than HCC metastases, making histopathological verification mandatory.
- Thoracoscopic(VATS)approaches effectively minimize operative morbidity and accelerate recovery in immunosuppressed transplant recipients.
- Conversion to mTOR inhibitor-based immunosuppression may improve survival outcomes in patients with metastatic HCC.
- Aggressive repeat metastasectomy is a viable strategy for achieving prolonged survival in recurrent disease.

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Ethics Committee Approval

This study was approved by the İnönü University Institutional Ethics Committee (Decision: 2025/7394, 25 March 2025).

Author Contributions

All authors contributed substantially to study design, data collection, analysis, manuscript composition, and final approval. Each author accepts responsibility for the integrity and accuracy of the work.

Conflict of Interest

The authors declare no competing interests.

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Artificial Intelligence Disclosure

We acknowledge the use of ChatGPT(GPT-4, OpenAI)solely for English language editing and grammatical

refinement. All scientific content, study design, data collection, analysis, interpretation, and conclusions were developed independently by the authors without artificial intelligence assistance

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