



## Analysis of Clinical Relevance and Predictive Factors for Postoperative Ascites after Liver Resection for Hepatocellular Carcinoma with Actual Long-Term Survival Analysis

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### ABSTRACT

**Background:** Ascites is one of the most common complications after liver resection. Although it is not generally considered to be an expression of postoperative liver failure, it is commonly associated with an increased rate of postoperative mortality. **Objective:** We evaluated the predictive factors and the clinical relevance of postoperative ascites, both for early and long-term results, using actuarial and actual long-term survival analysis. **Materials and methods:** A retrospective evaluation of 325 unselected and consecutive patients who received liver resection with hepatocellular carcinoma (HCC) was carried out. Overall survival and disease-free survival according to the occurrence of postoperative ascites were computed. **Results:** No features linked to the technical aspect of the resection had a predictive value. The only feature related to the tumor was the posterior location of HCC. In the subgroup of cirrhotic patients with a posterior-side HCC, the rate of ascites was 34.9%; 51 out of 57 patients with ascites (89.5%) presented a posteriorly located HCC in cirrhosis. Roughly one-fifth of patients with postoperative ascites presented signs of liver failure, but in-hospital mortality was almost four-fold that of patients without ascites. **Conclusion:** A posterior location of HCC significantly increased the risk of ascites.

**Keywords:** Liver resection, Hepatocellular carcinoma, Post-operative ascites

### INTRODUCTION

Ascites is a common complication after liver resection for cancer, with reported rates between 5% and 56% [1-3]. Although not included in the usual classifications of postoperative liver failure (PLF), ascites itself can lead to liver dysfunction, directly owing to the significant amount of protein-rich fluid lost into the abdomen, or indirectly precipitation septic complication [4-6]. The predictive risk factors of postoperative ascites have been studied in the literature; cirrhosis was recognized as the most powerful indicator in some heterogeneous populations of patients. Cirrhosis graded the risk of ascites according to the severity of functional damage [7-9]. Liver resection can hasten frail balance [7]. The parenchymal sacrifice increases the degree of functional impairment, lowering the oncotic power of blood. Furthermore, the acute phase after liver resection tends to involve edema in the interstitial organ space [9]; this factor and the reduced vascular bed following the amputation of parenchyma increases portal hypertension.

According to this hypothesis, a major liver resection, intraoperative transfusion, and the Pringle maneuver, which are often related to the appearance of ascites, act in a synergistic way to reduce liver function and increase portal hypertension [7,10]. Nevertheless, some clinical observations suggest that other factors also play roles that are not related to impair liver function. Clinical observations of ascites after small-liver resection are not rare (including laparoscopic enucleation) when the postoperative phase and liver function are completely normal. This topic suggests that liver resection itself and/or the intraoperative steps linked to the resection (mobilization of the liver, section of the ligaments, dissection of the pedicle structures with a lymphatic damage), working single or in tandem, may exacerbate the occurrence of ascites. In other words, ascites could partially reflect a technical problem. In that case, a different surgical procedure that focuses on lymphostasis might reduce the occurrence of ascites, thereby lowering the

perioperative risk. Furthermore, according to a recent paper on long-term results, postoperative ascites could increase the rate of recurrence of hepatocellular carcinoma (HCC), lowering overall survival rates [7].

This hypothesis was suggested on the basis of Kaplan Meier analysis, a common way to assess long-term results (i.e., generally 5 years after surgery). Nevertheless, as recently suggested, actual long-term survival at 10 years would truly be the most reliable parameter to consider clarifying if this postoperative complication might really lower the chance of long-term survival [11].

We carried out a retrospective study of our surgical series of patients with HCC operated until 2005. Our aim was two-fold. First, we evaluated the relative power of several clinical, anatomical, and technical features linked to the occurrence of postoperative ascites and the clinical value of ascites as a powerful index of postoperative morbidity and mortality. Next, we ascertained the relation between postoperative ascites and long-term survival using both actuarial and actual survival analysis.

## MATERIALS AND METHODS

Between 1992 and 2005, 325 patients received liver resection for HCC at the Surgical Clinic of the University of Brescia, Italy. Cirrhosis was found in 214 patients (65.8%). It was due to chronic viral infection in 180 patients (64 HBV-positive and 116 HCV-positive patients) and to alcohol abuse in 45 patients. All of the patients were children. For all the patients, we recorded the site of the lesions, distinguishing between the segments 2,3,4b,5,6 (99 patients) (i.e., the anterior segments) and cancer located in a posterior segment (4a,7,8 and caudate lobe) (226 patients). We also noted the main features of cancer (number of nodules, size). This anatomic classification was arbitrarily used to select the patients in whom a wide mobilization of the liver with the section of perihepatic ligaments was highly probable in order to expose the lesion. The technical aspects of the resection were noted (e.g., the occurrence of the Pringle maneuver, the need for transfusion, the type of resection (major and minor resection)). At the end of the procedure, a drain was left in the operative field of all of the patients. Ascites was defined as a daily drainage of more than 500 ml for at least two consecutive days. Postoperative liver failure was defined according to Balzan criteria (bilirubin >3 mg/dl and prothrombin index <50% or INR >1.7 at day 5) [12]. A follow-up evaluation was conducted as previously defined in the literature [13].

### Statistical Analysis

The differences in the demographic, etiological, clinical, and pathological features of HCC patients were tested using common statistical methods for mean and proportion comparisons. We collected data in Microsoft Excel (Windows, Microsoft Corporation, Washington). We compared discrete and continuous variables using the  $\chi^2$  test and the student's t-distribution, respectively. We modeled survival rates and curves using the actuarial method and compared them using a Mantel-Haenszel test. When the actual long-term results were examined, we assessed the results as a ratio of the number of still-living patients compared with all of the patients who received surgery at the beginning of the analysis. All of the tests were two-sided and were performed using  $p=0.05$  to reject the null hypothesis. All of the analyses were computed using the STATA version 12.0 statistical package (Stata Corporation, College Station, TX).

## RESULTS

We performed a minor resection (<3 segments) in the majority of the patients (82.1%). The Pringle maneuver was applied in 156 patients (48.0%); 61 patients (18.8%) were transfused during surgery. Postoperative ascites was observed in 57 patients (17.5%). Cirrhosis was the most powerful predictive factor for postoperative ascites; 52/214 cirrhotic patients (24.3%) presented ascites versus 5/111 non-cirrhotic patients (4.5%) ( $p<0.0001$ ). No feature linked to the technical aspect of the resection had a predictive value, including the width of liver resection, the need for

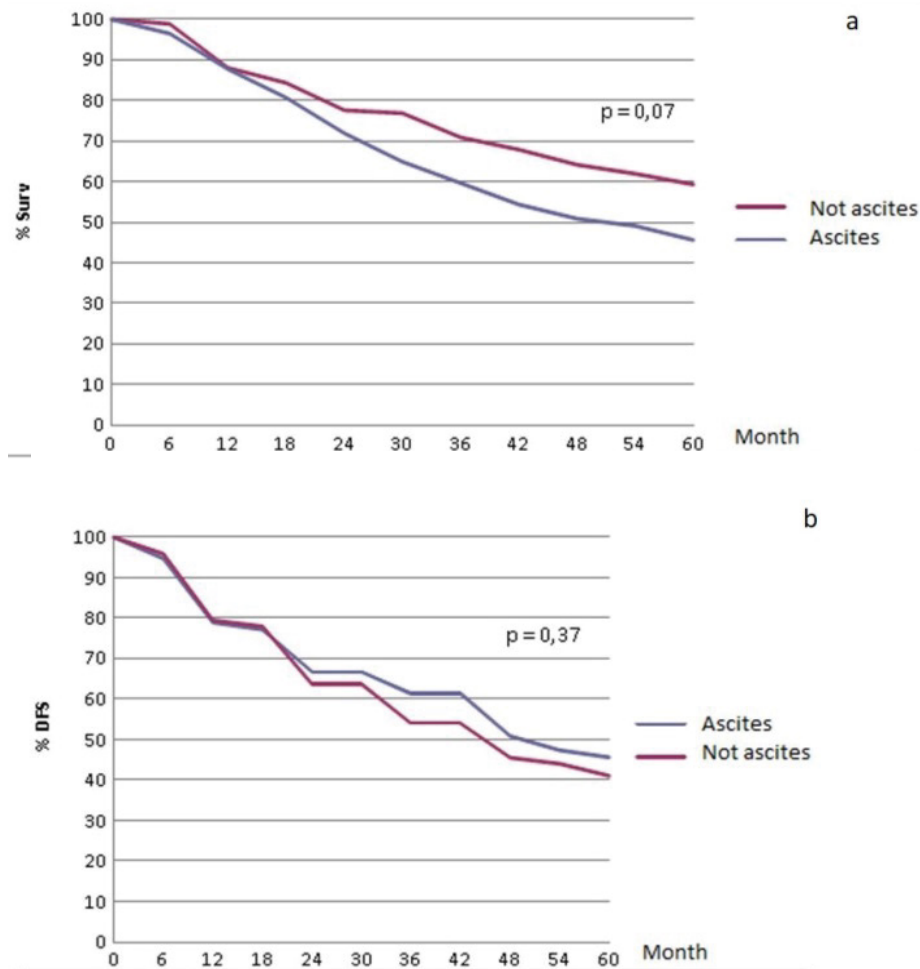
transfusion, or the Pringle maneuver. Among the features linked to a tumor, the only significant feature was the site of the HCC: ascites appeared in 22.6% patients bearing a posterior-sided HCC and in 6.1% of the patients with an anterior-located HCC ( $p<0.0003$ ). In the subgroup of cirrhotic patients with a posterior-side HCC (146 patients, 44.9%), the rate of ascites increased to 34.9%. In other words, 51 out of 57 patients with ascites (89.5%) presented a posterior-located HCC in cirrhosis (Table 1).

**Table 1 Demographic and tumor characteristics of patients according to postoperative ascites in 325 patients**

Variables		Ascites (n=57)		Not Ascites (n=268)		p-value
		n	%	n	%	
Age (years)	≤ 65	33	57.89%	134	50.00%	0.2800
	>65	24	42.11%	134	50.00%	
Sex	male	38	66.67%	218	81.34%	0.0140
	Female	19	33.33%	50	18.66%	
Cirrhosis	Yes	52	91.23%	162	60.45%	<0.0001
	No	5	8.77%	106	39.55%	
Size of Tumor	≤ 5 cm	37	64.91%	175	65.30%	0.6100
	>5 cm	30	35.09%	81	30.22%	
Number of nodules	1	39	68.42%	203	75.75%	0.1300
	>1	18	31.58%	58	21.64%	
Posterior segments	Yes	51	89.47%	175	65.30%	0.0003
	No	6	10.53%	93	34.70%	
Resection	Major	11	19.30%	47	17.54%	0.7500
	Minor	46	80.70%	221	82.46%	
Pringle	Yes	36	63.16%	120	44.78%	0.1400
	No	21	36.84%	109	40.67%	
Intraoperative transfusion	Yes	15	26.32%	46	17.16%	0.1100
	No	42	73.68%	222	82.84%	

Ascites was linked to concomitant signs of liver failure in only 11 out of 57 patients (19.3%). Therefore, ascites was associated with a normal index of liver function during the entire duration of the postoperative stay in the majority of the patients. Nonetheless, in-hospital mortality (16 patients, 4.9%) was significantly higher (12.2%) in patients who developed ascites compared with patients without ascites (3.4%) ( $p=0.004$ ). A long hospital stay (>15 days) was observed in 73.7% of patients with ascites and in 38.9% of patients without ascites ( $p<0.0001$ ). In the majority of cases, the long hospital stay was only related to ascites and the complications (transitory renal failure, pleural collection, electrolytic imbalance, contamination of peritoneal collection) were related to ascites; no patient was discharged with a persistent fluid loss.

Overall survival (OS) according to the actuarial method was 88.0%, 68.9%, and 56.9% at 1, 3, and 5 years. Disease-free survival (DFS) was 79.4%, 55.4%, and 41.8%. No statistical difference ( $p=0.07$ ) in OS was noted in patients with ascites (87.7%, 59.6%, and 45.6%, at 1, 3, and 5 years) or without ascites (88.3%, 70.9%, and 59.3%); at the same time, DFS was comparable between the two groups of patients (78.9%, 61.4%, and 45.6% versus 79.5%, 54.1%, and 41.0% at 1, 3, and 5 years, respectively) (Figure 1).



\*>500ml/day for more than 2 consecutive days

**Figure 1 Overall survival (a) and disease-free survival (b) according to the occurrence of postoperative ascites\* in a retrospective study of 325 patients**

The 10-year actual survival rate was 28.2%, and there was no significant difference between the patients with postoperative ascites (22.8%) and patients without ascites (29.9%).

In patients with HCC recurrence, a curative treatment of disease (liver resection, alcohol injection or radiofrequency ablation) was overall performed in 55.2% and 58.3% of patients, respectively, on the basis of the presence of a previous transitory phase of postoperative ascites.

## DISCUSSION

Our study revealed that ascites is common after liver resection for HCC. In 325 HCC patients, the rate of ascites was 18.5%, well within the 15% and 25.5% data reported by Ishizawa and Chan, respectively [3,7]. These patients must be considered to constitute a high-risk group; ascites is related to a nearly four-fold increase in in-hospital mortality. This result has a relevant clinical value. Ascites is not considered a sign of PLF, a definition that typically gives credit to the index of the synthetic power of the liver, such as prothrombin time and bilirubin levels [4,5]. Nonetheless, ascites is a powerful predictor of an ominous postoperative course; in these patients, the final event is almost always a liver failure, which can be secondarily evoked by problems (a necessity for diuretic therapy, renal failure, contamination of abdominal fluid) strictly related to the appearance and the management of ascites. Apart from this situation, ascites

is generally a transient complication. However, it also has a significant impact on hospital care, prolonging hospital stays due to the time necessary to control the fluid loss and the therapy of the complications that follow.

In 80% of our patients, ascites appeared without any sign of liver failure. We considered a threshold of 500 ml/day to be significant when the drain persisted for fewer days; we adopted one of the most restrictive definitions in the literature for postoperative ascites. At the same time, the drainage tube was retained, placed near the liver resection surface, until the fluid was <100 ml/day. Doing so we were able to conduct the analysis with the entire population of patients with this complication.

Studying the patients with postoperative ascites, we found only two parameters were directly positively correlated: the presence of cirrhosis and the posterior site (segment 1, 7-8 and 4a) of HCC. Cirrhosis per se was the primary reason for ascites: 52 out of 57 patients with ascites (91.2%) were cirrhotic. This relation appears clearly in the literature when HCC series are analyzed; on the contrary, metastases are the primary objective of surgery [9,10], the rate of ascites is very low because cirrhosis is virtually absent. A comparative evaluation among clinical series must consider both the relative rate of HCC and the incidence of cirrhosis. Furthermore, one must take into account that new etiologic factors have been considered, particularly within the last few years [14]. In our series of 685 patients, the rate of cirrhosis was 67.2% over the period 1992-2000 and 55.1% in the most recent period (data not shown).

If cirrhosis is the primary predictive factor of ascites, it is not enough to define a significant group of risk patients; only 24.3% of patients with cirrhosis suffered ascites after liver resection. Therefore, compensated cirrhosis per se is not sufficient to explain the appearance of ascites after surgery because the majority of patients did not suffer from this complication. Our study clearly demonstrated that other factors are important in this setting (first and foremost the location in the liver of the HCC). Up until now, the value of the site of HCC has never been clearly assessed. In our opinion, this datum reflects the importance of the anatomic and technical features linked to liver resection. The primary differences in the surgical approach between posterior and anterior HCC are the use of the Pringle maneuver and, above all, the wide mobilization of the liver and sectioning of the suspensory ligaments, which can be thickened with enlarged lymphatic channels inside. Liver mobilization is routinely performed to obtain better control over the confluence of the suprahepatic veins and to facilitate hemostasis during resection to reduce intraoperative bleeding. According to these data, ascites may be linked, at least partially, to this phase of surgery, evoking some “mechanical features” (e.g., the breakdown of the enlarged lymphatic vessels in the suspensory ligaments). This hypothesis is based on the fact that ascites was associated with any factors suggesting PLF in only 19% of cases.

Unlike the majority of literature results, we found no prognostic value of any other aspect linked to resection, such as the extent of liver resection (major versus minor resection), hemotransfusion, or the Pringle maneuver to affect the appearance of ascites after surgery [3,7,9]. These data is apparently difficult to explain and must be analyzed according to the surgical strategy adopted by the surgical team. We performed a low rate of wide resection (17.8%), following a restrictive policy towards a major hepatectomy in cirrhosis and selecting only the low-risk patients. At the same time, we are accustomed to using the Pringle maneuver selectively in many cases to make hemostasis easier. Therefore, in our experience, clamping is often a preventing measure and is not related to blood loss and the need for transfusion, features that, resembles the severity of the surgical trauma, could favor ascites. These aspects make it difficult to define the real role of these factors in the process of fluid formation after liver resection.

Our data do not confirm the adverse effect of ascites on long-term outcome, as suggested by Chan [7]. In reality, the characteristics of our study and those of Chan are not comparable for many reasons. First, in terms of the population of the patients, Chan’s findings related to a younger population was more than ours (mean age: 58 years vs 64 years). Furthermore, more than 60% of the Chan cohort was affected by HBV cirrhosis (46% in our dataset). Apart from this aspect, the difference in the results is largely due to the different types of postoperative ascites. In the Chan study, the reduced OS was entirely confined to the subgroup of patients with intractable ascites (ascites that required extended diuretic therapy for more than 6 months); in these patients, a rapid decrease in survival rate was observed just 1 year after surgery. This result is likely the expression of persistent reduced liver failure more than the expression of cancer recurrence. On the contrary, patients with a transitory ascites after surgery (“short-term ascites” according to

Chan's definition) had a survival rate comparable to that of patients without ascites despite a recurrence-free survival compared to the patients with intractable ascites. This result suggests that when ascites disappears, one's ability to curb the recurrence of cancer is not impaired and that long-term survival is not affected. Our study focused on a different group of patients who presented temporary ascites after surgery with a good response to medical therapy. These patients had a recurrence-free survival rate comparable to patients without ascites and the same rate of being cured given recurrence; their liver function was otherwise normal. These data, studied at the end of the actual survival, which included any cause of death, suggest that a transitory phase of ascites after surgery does not compromise the chance of long-term survival after liver resection for HCC. The strategy of curing recurring cancer must not change, even if the patients had suffered transient postoperative ascites. For these patients, an aggressive policy towards recurrence is the best way to ensure long-term survival [13,15]. The actual 10-year survival rate (28.2%) was nearly four-fold the value reported by Chen, which suggests the value of a multimodality strategy for curing such patients [7].

### CONCLUSION

In conclusion, our study confirms that ascites is a common complication after liver resection for HCC. Cirrhosis is the main predictive factor, but cannot explain per se this feature. Patients with an HCC located in the posterior segment of the cirrhotic liver suffered a high incidence of ascites; cancer location in the liver can be considered a risk factor as well, which suggests the value of some other technical aspects linked to the intraoperative phase. Ascites is not generally accompanied by symptoms of liver failure, but it marks a significant negative prognostic factor for postoperative mortality and morbidity. Long-term results due to the presence of postoperative transitory ascites, also evaluated with actual survival analysis, were not significantly different.

In the past few years, the IP has been raised as a global political issue that could undermine the efforts of governments to improve justice, access to care and policies for people in need. It is concluded that the IP, in any case, has a generally negative impact on the health system of countries that can affect patients and even service providers. It seems that strategies such as increasing knowledge of people, changing the culture, improving the quality of health services and careful monitoring of the delivery process, improving management, and transparency in payment participation systems, and using a legal approach can be effective in reduction of these payments.

### DECLARATIONS

#### Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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