

# Stress response to laparoscopic liver resection

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## Background:

The magnitude of the systemic response is proportional to the degree of surgical trauma. Much has been reported in the literature comparing metabolic and immune responses, analgesia use, or length of hospital stay between laparoscopic and open procedures. In particular, metabolic and immune responses are represented by measuring various chemical mediators as stress responses. Laparoscopic procedures are associated with reduced operative trauma compared with open procedures, resulting in lower systemic response. As a result, laparoscopic procedures are now well accepted for both benign and malignant processes. Laparoscopic liver resection, specifically, is employed for symptomatic and some malignant tumors, following improvements in diagnostic accuracy, laparoscopic devices, and techniques. However, laparoscopic liver resection is still controversial in malignant disease because of complex anatomy, the technical difficulty of

the procedure, and questionable indications. There are few reports describing the stress responses associated with laparoscopic liver resection, even though many studies reviewing stress responses have been performed recently in both humans and animal models comparing laparoscopic to conventional open surgery. Although this review examines stress response after laparoscopic liver resection in both an animal and human clinical model, further controlled randomized studies with additional investigations of immunologic parameters are needed to demonstrate the consequences of either minimally invasive surgery or open procedures on perioperative or postoperative stress responses for laparoscopic liver resection.

## Keywords

laparoscopic liver resection, surgical stress, minimally invasive surgery, immunology

## Introduction

Surgical stress causes a multitude of systemic responses. Overall, these responses to surgery are reflected in cytokine functions and cellular messenger systems. Many studies reviewing metabolic and immune responses, also called stress responses, have recently been performed in both humans and animal models comparing laparoscopic to conventional open surgery [1–12]. These articles described a diminished stress response following minimally invasive procedures by avoiding a substantial abdominal incision, and the ensuing tissue damage. Postoperative immunocompetence is evaluated by measuring levels of interleukins (IL-1 $\beta$ , -2, -6, -8, -10, -12), tumor necrosis factor alpha (TNF- $\alpha$ ), adrenocortical hormones, C-reactive proteins (CRP), and peripheral lymphocytes, and by performing delayed-type hypersensitivity (DTH) skin tests [13, 14]. In particular, IL-6 production and activation (by monocytes, macrophages, and endothelial cells) herald an early host response to surgical trauma. Subsequently, increased

serum IL-6 levels are believed to correlate with the magnitude of associated tissue injury [15].

The laparoscopic approach has been well accepted for solid organ resection, including spleen [16], kidney [17], adrenal glands [18], and more recently the liver [19–21]. These advances are multi-factorial, and include development of safer techniques, better instrumentation, and laparoscopic devices which provide improved visualization. The result of these developments may be to preserve immune function after surgery as a result of smaller incisions, a reduction in tissue injury, and less blood loss (avoiding transfusion).

Laparoscopic liver resection has developed more slowly because of challenges in diagnostic accuracy, complex anatomy, and perceived technical difficulties. The first laparoscopic liver resection was reported by Gagner *et al.* in 1992. This group performed a laparoscopic non-anatomical partial liver resection of a 6-cm, focal nodular hyperplasia using an ultrasonic dissector, monopolar cautery, and clip appliers [19]. Buscarini *et al.*, in 1995, reported that laparoscopic use of radiofrequency (RF)

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hyperthermia to resect a small hepatocellular carcinoma (HCC) was feasible and safe [22]. However, this method is not indicated for large tumors over 4 cm. In 1996, Azagra *et al.* performed a laparoscopic anatomical left lateral segmentectomy of a symptomatic adenoma [21]. Nevertheless, laparoscopic liver resection remains at the phase I/II trial stage. Recently, three European multi-center studies were published regarding the feasibility of laparoscopic liver resection [23–25]. Their results suggest that laparoscopic liver resection is safe and feasible for selected malignant and benign tumors.

We herein describe that laparoscopic liver resection may be associated with a diminished stress response when compared with open liver resection in an animal model. There are few reports in clinical settings to support a diminished stress response following laparoscopic liver procedures. Currently, we can describe postoperative stress response following open procedures and assess reduction in perioperative or postoperative stress after laparoscopic procedures.

### **Surgical technique and stress response to laparoscopic liver resection in an animal model**

Several studies have shown diminished stress responses following laparoscopic surgery, including cholecystectomy [6–8], colectomy [9–11], and distal pancreatectomy [4]. Most of the reports demonstrated that laparoscopic procedure is associated with reduction of surgical stress as compared with that of open surgery. However, there has been less written about the stress responses to laparoscopic liver surgery.

Kurian *et al.* reported a series of hand-assisted laparoscopic donor hepatectomies for living related transplantation (LRLT) [26]. That group performed a hand-assisted method with the Dexterity Pneumosleeve device (Dexterity Surgical, Inc., Roswell, GA, USA). Their surgical devices included electrocautery, the harmonic scalpel (Ethicon Endosurgery, Inc., Johnson & Johnson, Cincinnati, OH, USA), the laparoscopic Cavitron ultrasonic surgical aspirator (CUSA; Valleylab, Boulder, CO, USA), and the Endo-GIA II stapler (USSC, Norwalk, CT, USA). In particular, they described the effectiveness of the laparoscopic CUSA used in connection with the harmonic scalpel. The endostapler was particularly useful for dividing hepatic

parenchyma and large hepatic vessels to minimize bleeding from the resected edge. As a result, liver function tests were within the normal range during the postoperative period. This study concluded that hand-assisted laparoscopic donor hepatectomy for LRLT was feasible and safe.

Burpee *et al.* investigated the metabolic and immune response to laparoscopic and open liver resection using a porcine model [27]. They performed a left lateral segmentectomy using either a laparoscopic or open approach and assessed stress responses, measuring CRP, serum cortisol, TNF- $\alpha$ , IL-6, and DTH skin testing. There were no significant differences in operative time, specimen weight, or estimated blood loss in this study (Table 1). There were also no significant differences in postoperative liver function test results between the two groups. Both serum cortisol and CRP were slightly higher in the open liver resections, but these differences did not achieve statistical significance. The mean TNF- $\alpha$  levels were significantly more elevated in the open group after 48 hours, and this continued for up to 1 week after surgery. The mean IL-6 levels also were significantly higher in the open group at 3 and 24 hours after incision. Animals in the laparoscopic group had a significantly greater response to DTH testing than those in the open group 48 hours after surgery, which suggests greater preservation of immune response after laparoscopy (Table 1). Moreover, there were significantly fewer adhesions in the laparoscopic group 6 weeks postoperatively. Whawell *et al.* have reported that the fibrinolytic response is regulated by a number of cytokines including IL-1, IL-6, and TNF- $\alpha$ , each of which increase plasminogen activator inhibitor 1 (PAI-1) secretion from mesothelial cells, and enhance fibrin deposition [28]. Disparities in the inflammatory cytokine response between laparoscopic and open surgery may account for differences in adhesion formation.

**Table 1.** Stress response to laparoscopic vs open liver resection

Parameter	Laparoscopic group	Open group	p value
Specimen weight	180 ± 16 g	201 ± 30 g	0.13
Estimated blood loss	114 ± 24 ml	189 ± 88 ml	0.14
Operative time	100 ± 22 min	100 ± 24 min	0.6
DTH skin testing	20.7 ± 2.7 mm	14.1 ± 1.5 mm	0.0001

DTH, delayed-type hypersensitivity. Adapted from Burpee *et al.* [27] with permission.

### **Clinical benefits using laparoscopic liver resection to diminish the stress responses**

Surgical stress is impacted both by the procedure performed and by operative variables such as procedure length and blood loss. The body's response to stress is multi-functional, and includes neuroendocrine, immune, metabolic, and cytokinetic responses. Several reports have evaluated immune reactions after open hepatectomy. Badia *et al.* reported on hepatic resection with total vascular exclusion with regard to measurement of systemic cytokine response including endotoxin, interferon- $\gamma$  (IFN- $\gamma$ ), TNF- $\alpha$ , IL-1, and IL-6. As a result of this study, endotoxin concentration was raised both before and postoperative period. TNF- $\alpha$  concentrations were undetectable. IFN- $\gamma$  and IL-1 responses followed a low and inconclusive pattern. IL-6 was significantly increased from 6 hours after operation to the third postoperative day, peaking at  $699 \pm 277$  pg/ml at 24 hours ( $p < 0.01$ ) [29]. The two of 13 patients who died had the highest postoperative concentrations of IL-6. They concluded that treatments that minimize the IL-6 response to major hepatic resection might be of value.

The IL-8 levels immediately after hepatectomy correlated with the operative time, blood loss, and volume of blood transfusion, postoperative fever, leukocyte count, and bilirubin value. Thus interleukins may be an accurate indicator of surgical stress. IL-10, an anti-inflammatory cytokine, was also elevated in both the blood and peritoneal fluid after hepatectomy [30].

Laparoscopic liver resection has recently been shown by several groups to be feasible and safe [21, 24, 25, 31]. Although some advantages of laparoscopic procedures include reduced postoperative pain and shorter recovery time, the operative technique used for laparoscopic liver resection is almost the same as in open surgery. Opioid use postoperatively provides an assessment of procedure-related pain. Mala *et al.* [23] reported that opioids were required for a median of 1 day and, especially, three patients did not need such analgesia on the first operative day at all in 15 laparoscopically resected patients. On the contrary, in open resection 5 patients undergoing 14 procedures were needed for median 5 days (laparoscopic vs open:  $p = 0.001$ ). Moreover, median postoperative hospital stay was 4 days for patients undergoing laparoscopic liver resection compared with 8.5 days for those undergoing open resection in this series ( $p < 0.001$ ).

There are few reports in clinical settings to support a diminished stress response following laparoscopic procedures using stress response mediators.

Reports of laparoscopic liver resection are listed in Table 2. Preoperative imaging using helical computed tomography, MRI, and scintigraphy helped to identify appropriate patients for resection. Almost all patients underwent non-anatomical liver resections: segmentectomy, subsegmentectomy, and left lateral segmentectomy. Major hepatectomy was performed in 6 cases (6/215, 2.8%) [24, 25, 32]. The conversion rate to an open procedure was 13.2% (20/152) and the blood transfusion rate was 8.2% (14/171). Estimated blood loss was the same or less than in conventional open surgery and postoperative hospital stay was shorter (Table 2) [21, 23–25, 31–38]. These reports also noted that laparoscopic procedure for liver resection required special equipment, and advanced experience and techniques.

Intraoperative laparoscopic ultrasonography, particularly flexible type, can be useful to demonstrate the lesion accurately, to determine its relation to vascular structures, and to guide the resections. Using this device, it may be possible to avoid tumor transection and gain enough free margins.

The argon beam coagulator and the ultrasonic dissector are available for liver resection to secure hemostasis of the transaction plane. However, argon beam gas carries the risk of gas embolism [39]. Endostaplers are effective for large vessels and parenchyma.

Liver surgery has several problems in comparison to that of other organs. A major problem in liver resection is the control of bleeding, because the liver is one of the vascular-rich organs. Wedge resection is not so problematic as regards bleeding, because of improvements in hemostasis devices such as the ultrasonic dissector for small vein or biliary elements, and the argon beam coagulator and/or fibrin glue sealant for parenchymal tissue. However, anatomical resection can be associated with significant operative blood loss and the need for transfusion of blood and blood products, exposing the patient to the risks of transfusion and delayed postoperative recovery. Moreover, occasionally postoperative morbidity and mortality of hepatic resection correlate closely with operative blood loss [40]. To prevent this bleeding, the Pringle maneuver, which involves temporary occlusion of the hepatic artery and portal vein, can be employed for liver anatomical resection in particular.

**Table 2.** Summary of laparoscopic liver resections

Author [Ref]	Year	Number of patients	Procedure	Special devices and methods	Operating time (min)	Conversion	Blood loss (ml)	Transfusion	Postoperative stay (days)
Azagra et al. [21]	1996	1	Left lateral segmentectomy	Irrigation suction device Autotransfusion device	390	None	600	NR	NR
Watanabe et al. [32]	1997	1	Left lateral segmentectomy	Abdominal wall lifting method	NR	None	120	NR	13
Samama et al. [33]	1998	4	Left lobectomy	CUSA, intermittent clamping	180–300	None	NR	NR	6.3 (4–10)
Rau et al. [34]	1998	17	Segmentectomy Left lobectomy	CUSA, water-jet cutter	110–275	1/17	458 ± 344	1/17	7.8 (2–39)
Descottes et al. [31]	2000	16 (17 tumours)	Non-anatomical segmentectomy Left lateral segmentectomy Right hepatic lobectomy	Ultrasonic dissector, triad clamping (straight clamp with toothed sides)	115–585	None	NR	None	5.3 (2–15)
Cuschieri [35]	2000	9	Segmentectomy Left lobectomy Radiofrequency ablation	HALS	60–360	NR	800	NR	4 (3–6)
Fong et al. [36]	2000	11	Segmentectomy Left lateral segmentectomy	HALS	143–358 (248)	6/11	NR	NR	5
Shimada et al. [37]	2001	18	Segmentectomy Left lateral segmentectomy	Abdominal wall lifting method	214–430 (325)	None	400 (188–1050)	1/17	12
Gigot et al. [24]	2002	37	Wedge resection Segmentectomy Left lateral segmentectomy Major hepatectomy	Ultrasonic dissector, endostapler, argon beam coagulator, atraumatic Lucane liver clamp	NR	4/37	≥500 in 5 patients	6/37	6 (2–16)
Mala et al. [23]	2002	13	Sub-segmentectomy Left lateral segmentectomy (bisegmentectomy) Cryoablation	CUSA	80–334 (187)	None	600 (100–3300)	1/13	4 (1–6)
Descottes et al. [25]	2003	87	Wedge resection Segmentectomy Left lateral segmentectomy (bisegmentectomy) Major hepatectomy	Endoclip, endostapler, ultrasonic dissector	NR	9/87	604 (321–900)	5/87	5 (2–13)
Inagaki et al. [38]	2003	1	Left lateral segmentectomy	HALS, Pringle maneuver	295	None	500	None	13

NR, not reported; CUSA, cavitronic ultrasound surgical aspirator; HALS, hand-assisted laparoscopic surgery.

This clamping technique allows transaction of liver parenchyma with minimal blood loss and adequate hemostasis of the transaction plane, and is far less stressful for the surgeon.

The laparoscopic approach carries an increased risk of

gas embolism compared with the open approach. During the dissection, when risk is present, the pneumoperitoneum pressure is decreased to 6 mmHg and the responsive vein to the dissection area is occluded by Teflon tourniquet. These procedures allow the surgeon

to minimize the risk of gas embolism, an accident that has been described in conventional surgery [41].

The steps in the video-assisted approach correspond to those of the complete laparoscopic approach, except that further procedures carry a risk of gas embolism, such as parenchymal dissection and hepatic venous embolism, for example, when using abdominal wall lifting without carbon dioxide insufflation.

Hand-assisted laparoscopic surgery (HALS) is different from total laparoscopic surgery because the assisting hand of the surgeon is used for display, exposure, palpation, gentle retraction, and blunt finger dissection during the operation; it also provides immediate hemostasis in the event of intraoperative bleeding [36]. A variety of hand-access devices has been used. On the other hand, possible disadvantages of HALS include possible obstruction of the visual field by the surgeon's hand during the operation, and also a slightly longer incision scar, which is almost comparable to the operative scar in a mini-laparotomy operation. Visual obstruction may be minimized by marking the appropriate incision and port sites.

As a result of the development of devices and improvement of techniques, laparoscopic liver resection may be available, and it may also produce less discomfort for patients.

## Conclusion

Patient selection is essential for safe laparoscopic resection of the liver. The patients best suited for laparoscopic resection are those with tumors at the inferior edges of the liver or with tumor confined only to the left lateral segment; easier access to the tumor and better retraction in these areas makes resection more feasible. Conversely tumors in segments IVa, VII, or VIII are poor candidates for laparoscopic resection because these tumors near the dome of the liver are more difficult to expose. Vascular injury during parenchymal transaction is a major concern.

The laparoscopic procedure is very similar to the open procedure. Laparoscopy may contribute to reduced operative time and perioperative blood loss, and lead to diminished surgical stress because of development of devices, improvement of procedures, and advanced techniques. Although stress responses have already been confirmed in an animal model, further randomized

controlled trials with additional investigations of immunologic parameters may be needed in the clinical setting to assess surgical stress for laparoscopic liver resection.

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