Chapter

Surgical Therapy of Hepatocellular Carcinoma: State of the Art Liver Resection

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Abstract

Hepatocellular carcinoma (HCC) represents the third most common cause of cancer-related death, showing incremental growth rates throughout the last decades. HCC requires multidisciplinary approach in a group of patients suffering from underlying chronic liver disease, usually in the setting of cirrhosis. The mainstay of treatment in resectable cases is surgery, with anatomic and non-anatomic liver resections widely implemented, as well as liver transplantation in well-selected individuals. Nowadays, there is a variety of liver parenchyma transection devices used by hepatobiliary surgeons in specialized centers, which has significantly improved postoperative outcomes in HCC patients. Therefore, hepatectomy is considered safe and feasible and should be the main therapeutic option for HCC patients, candidates for resection. Liver resection utilizing cavitron ultrasonic aspirator in combination with bipolar radiofrequency ablation is safe and effective for the treatment of HCC with favorable clinical and oncological outcomes.

Keywords: Hepatocellular Carcinoma, cirrhosis, surgical treatment, liver resection, technique, outcomes

1. Introduction

The evolution and development of the surgical techniques utilized during liver resection for Hepatocellular Carcinoma (HCC) are largely an account of the efforts to minimize bleeding during liver parenchymal transection. There is a close relation between blood loss and unfavorable outcomes during liver resection. The modern era liver transection techniques are based on notable advances in solid organ imaging (Computed Tomography, Magnetic Resonance Imaging, Ultrasound), vastly improved anesthetic management, enhanced knowledge of segmental liver anatomy as described by Couinaud [1], refined surgical techniques with notable appreciation of the functional reserve of the liver remnant, as well as the liver regeneration process [2].

Major hepatectomies had been associated with mortality rates of up to 20% during 1990's, and excessive bleeding was an important and common cause of operative mortality [3]. However, liver resection can now be accomplished with mortality rates of less than 2% in most specialized hepato-pancreato-biliary (HPB) centers [4].

While better patient selection and improved assessment of functional liver remnant are important factors [5], reduced blood loss and the diminishing need for blood transfusion have been additional reasons for improved peri-operative outcome [6]. Other advances in operative technique, including improved delineation of the optimal transection plane with intra-operative ultrasound [7] and the benefit of intermittent inflow occlusion, have also contributed to a reduction in blood loss during major liver resections [8].

The technique of parenchymal transection in hepatic resection has been a topic of great debate for decades worldwide. Finger fraction and clamp-crush techniques have been presented more than fifty years ago and have established as standard approach for liver transection. Significant technological improvements over the past thirty years have led to utilization and adoption of specific surgical instruments and devices for liver transection, such as radiofrequency ablation (RF), ultrasonic cavitron aspirators (Cusa), bipolar sealers (Aquamantis), bipolar energy devices (Ligasure), ultrasonic dissectors (Harmonic), water jet and Tissue link, amongst others [5, 9, 10].

2. Prehistory of liver surgery (1886–1950)

Liver surgery has been a huge chapter in modern surgery and more groundbreaking evolution is still yet to come. Its meaningful to review the beginning of hepatic resections that were reported in the 19th century and follow the journey up to modern times and the techniques that are used today.

The first hepatic operation was done and reported back in 1886 by Lius. He achieved the first partial hepatectomy to a patient with a hepatic adenoma. Reportedly, the use of sharp instruments and Paquelins cautery were utilized for this operation. Unfortunately, post -op hemorrhage was uncontrollable, and the patient died. It is interesting to note that even back in the 19th century, the use of cautery by liquid means was prominent [11].

Following the pioneer of hepatic surgery, Bruns (1888- metastatic liver cancer) and von Eiselberg (1893-hemangioma) attempted hepatectomies. Furthermore, Keen described in 1899 a liver wedge resection in 3 of his patients [12]. In 1891 Lucke achieved the first successful left lobar liver carcinoma excision [13]. In 1908 a very famous physician, whose technique is predominantly used around the world today in hepatic operations, Doctor Pringle, performed abdominal operation in 4 patients with hepatic bleeding of traumatic cause. He managed to control the hemorrhage by clamping the hepatic vein and artery. Only 1 patient survived after this maneuver [14].

In 1911 Wendel reported the first successful right hepatectomy in a 44-year-old woman. He followed the instructions of Cantlie's functional anatomy in detail. Primarily hilar dissection and ligation of right hepatic artery and right hepatic duct was achieved, and furthermore dissection through the quite avascular plane described by Cantlie was performed. Only a year later, Lin applied a new technique. The goal was to resect and destroy liver parenchyma with minimal damage to vessels. This concept will be followed over the years up to present times. The use of the "finger fracture method" served such purpose by resecting parenchyma and leaving vessels undamaged and ready for ligation [15].

As years passed by, it is more evident that 5 historic factors from 1950 and onwards played a role and shaped liver surgery, especially for hepatocellular carcinoma, as we know it today. Primarily the ability of bleeding control in liver trauma gave confidence to surgeons to proceed in large resections. Secondly, the control of blood supply and drainage of the liver to a more specific level rather than gross ligation of large vessels. The advance in supportive medicine such in fluid balance, adequate anesthesia, respiratory support, and hemodynamics played a key role in a successful operation. Following these, the advancement of imaging modalities and the multimodality team approach in treatment algorithm of HCC.

3. Multi-modality treatment of HCC

HCC remains the leading cause of cancer related mortality worldwide [16]. Hepatitis C is the most frequent risk factor for HCC in the Western world. On the other hand, chronic hepatitis B infection is the main risk factor in East Asia and sub-Saharan Africa, where incidence rates of HCC are the highest [17]. The MDT can establish patient access to well-established, as well as new multimodality therapies, consulting with all the involved specialists. These emerging therapeutic algorithms have led to review and updates of the treatment management in primary hepatobiliary cancers. Surgery remains the most-effective curative option for all primary hepatobiliary cancers; however, not all patients are good surgical candidates at the diagnosis, due to advanced disease. The Hepatobiliary MDT is crucial for ensuring that other treatment modalities are considered (palliation – best supportive care). This approach can optimize patient care, both on curative and palliative ways. HCC screening has undoubtedly helped earlier detection of tumors, allowing prompt commencement of treatment, positively impact on patients' outcomes [18].

4. Evolution of imaging modalities

Although current management guidelines for HCC do not require biopsy to prove the diagnosis, lesions greater than 2 cm on MRI or Computed Tomograph Angiography (CTA) scans, with elevated AFP (more than 400 ng/mL) or AFP incrising within sequential measurements, do not require pathologic confirmation according to the guidelines of the European Association for the Study of the Liver (EASL) [19].

According to American Assosiation of Liver Diseases (AASLD) guidelines, liver nodules detected on abdominal US, measuring less than 1 cm should be re-examined twice a year. If no radiological alteration of the hepatic lesion has occurred during a period of up to 2 consecutive years, routine surveillance should be considered.

Every suspicious lesion in high-risk population, with suggestive US-findings for HCC, should be further studied with additional imaging modalities. This radiology workup should include a 4-phase multidetector CT scan or dynamic contrast enhanced MRI. If the tumor has all the typical characteristics of HCC, it should be treated as HCC. If a liver nodule compatible with HCC is greater 2 cm at the initial diagnosis after one dynamic imaging study, biopsy is not mandatory. However, if the vascular profile of the lession on imaging studies of a non-cirrhotic patient is not compatible with HCC, a second imaging study or biopsy of the lesion should be performed to secure the correct diagnosis. If the biopsy is negative for HCC, patients should be further surveilled *via* an abdominal US every 3–6 months, until the lession presents enlarged or with altered imaging characteristics. According to the guidelines of the Asia-Pacific Association for the Study of the Liver 2010 [20], every liver lesion with non-typical vascular features should be further investigated with other modalities, such as endoscopic ultrasound (EUS).

It is well established that contrast-enhanced CT scans and MRI scans can be performed to examine, differentiate, and investigate a liver lesion. HCC has commonly a unique imaging array [21]. High arterial-phase contrast uptake followed by rapid washout in late phase are common in contrast-enhanced CT and MRI scans; these characteristics may not be present in earlier stages or in not well-differentiated tumors. Triphasic CTA can identify more lesions; however, in patients with nodular cirrhosis, contrast-enhanced MRI should be performed. Tumors sizing between 1 and 2 cm in cirrhotic patients, should be further studied with triphasic CTA and MRI to exclude HCC [22].

5. Anesthesiology management

During the last century, huge technological and medical advance aid surgeons to easier define their objective rather carefully and to overcome the shrieks and wails of their awake patients as in past times. Anesthesia of modern times came of age, so that the operating rooms became well-orchestrated exhibitions of joint expertise and support. We can now safely say that all matters are now a concern of the anesthetists; they furnished the hemodynamic support for complex operations, as liver surgery. Consequently, surgeons were allowed to focus on their meticulous procedures.

Matters of special interest are conditions that can cause an elevation of right-side cardiac and central venous pressure (CVP), which can significantly increase the risk of intra-operative bleeding. Invasive arterial and CVP monitoring allows for better hemodynamic control and regular blood sampling. All patients may benefit from cardiac output monitoring, enabling greater stability during the cardiovascular changes associated with vascular occlusion during hepatic resection. Core temperature should be monitored and normothermia maintained using warmed-fluids and forced warm-air blankets. Intra-operative coagulation profile should be monitored and corrected with fresh frozen plasma or/and coagulation factors, as indicated from laboratory results. Neuromuscular block should be also monitored [23].

6. Surgical approach

It well established that in patients without impaired underlying liver status (cirrhosis), an anatomical resection should be accomplished. Major hepatectomies can include up to two-thirds of the functional parenchyma. For cirrhotic patients, due to impaired liver regeneration process, resection is generally minimized to smaller hepatectomies, to maintain adequate liver function. Hypertrophy of the future liver remnant can be achieved with the use of pre-operative portal vein embolization (PVE).

One of the most important key factors during liver resection of HCC is the utilization of intra-operative ultrasound (IOUS), to identify tumor location, margins and its relation to the inflow and outflow vascular structures. The definition of a proper surgical strategy is important not only for achieving an adequate tumor-free margin, but also for avoiding inadvertent injuries to major intrahepatic vessels or bile duct pedicles during dissection or resection.

Management of hepatic inflow through the portal vein and/or vena cava, and hepatic outflow through the hepatic veins, can be routinely performed with control of this vessels. Controlling of the vascular inflow (Pringle maneuver) as an alternative to total vascular occlusion, has decrease deleterious effects of liver ischemia. Ischemic preconditioning of the liver has recently been proposed as a hepatoprotective measure, consisting of application of a brief period of ischemia (10 min) and reperfusion (10 min) after which, a prolonged-period of the liver inflow occlusion can be safely supported. In a prospective series, comparing major liver resections using the Pringle maneuver lasting 30–60 min, an advantage was found of ischemic preconditioning in young patients (<60 years), as well as in patients with steatosis or cirrhosis. Intermittent Pringle occlusion can be well tolerated by cirrhotic patients for up to 60 minutes, and is better tolerated than continuous clamping. The use of low CVP (less than 5 mm Hg) is also of great importance.

7. Techniques of liver parenchyma transection for HCC

7.1 Finger fracture technique

Hepatic transection remained a challenge for all surgeons, for more than a century. The first scheduled hepatectomy was performed in 1888 from Carl Langenbuch [24]. Liver surgery was minimal thus, up to the 20th century, when Pringle maneuver was first presented, for bleeding control during emergency hepatic resections [14]. Hepatectomy is particularly difficult in cirrhotic liver due to the fibrotic nature of liver tissue. The finger fracture technique, the liver tissue is fractured and crushed by the thumb and index finger followed by isolating and ligating the resistant intrahepatic vascular and ductal structures [15].

7.2 Crash-clamp (Kelly) technique

The finger fracture technique, in which the parenchymal transection is done by crushing the parenchyma between the thumb and another finger isolating vessels and bile ducts which were ligated and divided, after liver inflow occlusion, was afterward improved using a surgical instrument such as the Kelly clamp [25]. Using the Kelly clamp technique during hepatic resection of cirrhotic liver with HCC can be performed in less operative time, while help obtaining a clearer operative field [26].

7.3 Radiofrequency ablation (RFA) assisted technique

RF assisted hepatectomy, for the treatment of hepatocellular carcinoma amongst other liver malignancies, was first implemented by Habib's group at Hammersmith Hospital, London, UK [27]. Ever since, RFA has been widely used for the in-situ ablation of unresectable liver and other solid organ tumors [28], but it has now been incorporated into routine liver resection, being used to create a line of coagulative necrosis that can subsequently be divided with a scalpel with relatively little blood loss [29]. In recent years, the continuous use and development of RFA ablation in liver surgery have produced satisfactory results in the treatment of small HCC. It can also block small and medium-sized blood vessels in the liver through thermal coagulation, so it has been used in liver resection to reduce bleeding. However, the use of this technique remains controversial due to reported perioperative outcomes and complications; some studies have reported that radiofrequency-assisted liver resection causes severe postoperative liver dysfunction, and the incidence of postoperative complications is higher than that of simple hepatectomy [30].

7.4 Cavitron ultrasonic aspirator (CUSA) technique

Cavitron Ultrasonic Surgical Aspirator (CUSA), also known as Ultrasonic Dissector, was first popularized by Hodgson et al. in 1979 [31]. The ultrasonic waves generate energy to fragment and aspirate parenchymal tissue. Contact of the oscillating titanium tip instigate fragmentation of hepatocytes owing to the high-water content while, selectively sparing the blood vessels and bile ducts because of poor tissue water content. In the liver parenchyma, anatomically, both the Glissonean cords as the inflow system and the hepatic veins as the outflow system show branching, like a tree. Both systems rise from the dorsal side, where they are relatively close to each other, and branch towards the ventral side. Any liver resection can become simpler and safer by selectively dissecting in a plane, where no Glissonean cord runs, such as an intersegmental plane. When such planes are dissected with the CUSA, the hepatic veins, which are relatively thicker and can be more easily identified than those that appear when the other parts are divided, usually appear in the cutting plane. Further, some thinner branches, which cross the cutting plane and flow into the exposed thicker hepatic vein, should be cut at the confluence without incurring a split injury [32]. It has been proven that CUSA selectively destroys and aspirates parenchyma, leaving vessels and biliary ducts almost intact with larger vessels and large intrahepatic bile ducts amenable to ligation or clipping [33].

7.5 Sealing device-assisted technique

The LigaSure Vessel Sealing System (Valleylab, Boulder, CO, USA) is a hemostatic and dissecting tool, which is able seal blood vessels (up to 7 mm in diameter), by denaturing collagen and elastin within the vessel wall and in the surrounding connective tissue [34]. LigaSure can be safely applied in any type of liver and hepatectomy combined with the crush clamping method.

The Harmonic Scalpel (Ethicon Endo-Surgery, Cincinnati, OH, USA), utilizes ultrasonic vibration of two blades causing destruction of hydrogen bonds. This disturbance of hydrogen bonds causes protein denaturization coagulating small vessels of 3 mm diameter. The parenchyma is then transected with blade movement in a saw-like fashion [35].

7.6 Tools for resection

As mentioned above, the techniques used in liver transections were described in reports and were widely used. From the finger fracture technique described by Lin [15] to the use of the blunt end of a hemostat by Ogilvie [36] and the use of the blunt edge of a scalpel by Quattlebaum, a common goal can be perceived. The identification of different tissues, parenchyma vs. vessel, via the means of blunt dissection. Perseverance of great vessels and following appropriate ligation was the main aim of hepatic surgeons to avoid uncontrollable hemorrhage. Avoiding such complication could mean avoiding death.

In 1928 the first electrocautery device was invented. The Bovie knife, known from its inventors Bovie and Cushing, is the tool of choice up to this day by majority of centers when it comes to hemostasis and partial resection of the liver parenchyma [37]. A few years later, the need of new and perhaps more effective ways for liver surgery was explored.

Another technique that originates from compression characteristics of hemostasis is the hemostatic clamp. During the years, many surgeons have used such clamps. Back in 1960s the first clamp used in liver surgery was described by Stucke [38]. Variation of such were seen within the same decade. It needed the efforts of Nakayama to reach a newly designed clamp, specific to the liver [39].

8. Our technique

We have been performing liver resection routinely for the past 30 years. The first attempt towards a bloodless and uneventful hepatectomy was the formation of a proper HPB Unit, formed by specialist surgeons, dedicated anesthetists, ICU beds and experienced radiologists (invasive). Gradual implementation and enhancement of the new techniques followed. In the beginning, finger fracture/crash clamp technique was performed in all cases of liver resection, with the addition of electrocautery and argon beamer as adjuncts. Following that, from the beginning of 2000s, we adopted and evolved the RF-assisted liver resections, with favorable outcomes during numerous hepatectomies. However, we moved to the two surgeons' technique with newer abdominal retractors (Thompson Liver / Oncology System) since 2006; our transection tools have been standardized to implementation of CUSA for dissection of liver parenchyma and Aquamantis for hemostasis (**Figures 1** and **2**).

For major hepatectomies the ipsilateral major hepatic veins were encircled within vessel loops. When an anatomic resection was planned, hilar dissection was performed (**Figure 3**).

The ipsilateral branch of hepatic artery, portal vein, and common bile duct were encircled within vessel loops, but not divided, until the parenchymal dissection reached that point. Hilar dissection was not performed for non-anatomical hepatectomy. During major hepatectomies, the ipsilateral hepatic artery, portal vein branches and bile duct branches were ligated intra-hepatically during parenchymal transection. In addition, for major hepatectomies, the major hepatic veins were either suture-ligated and divided or divided using endovascular staplers at the end of parenchymal transection (**Figures 4–8**).

Drains are routinely placed in all patients.

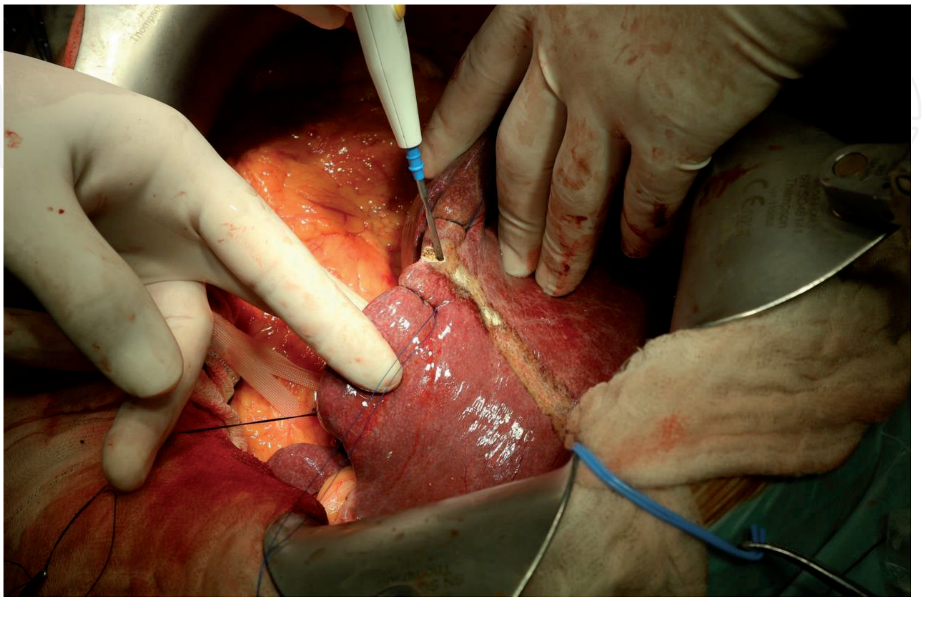

Figure 1.
Demarcation line using monopolar cautery.

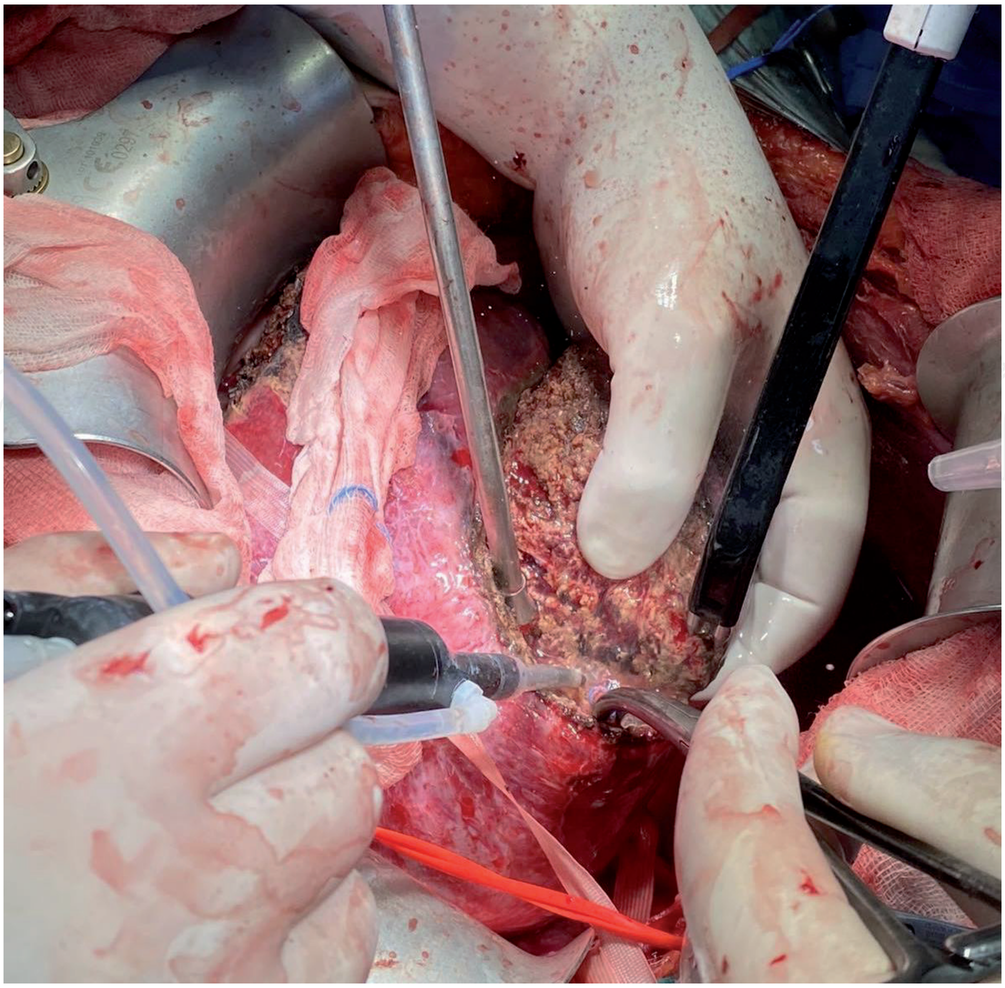

Figure 2.
Liver transection with CUSA and Aquamantis.

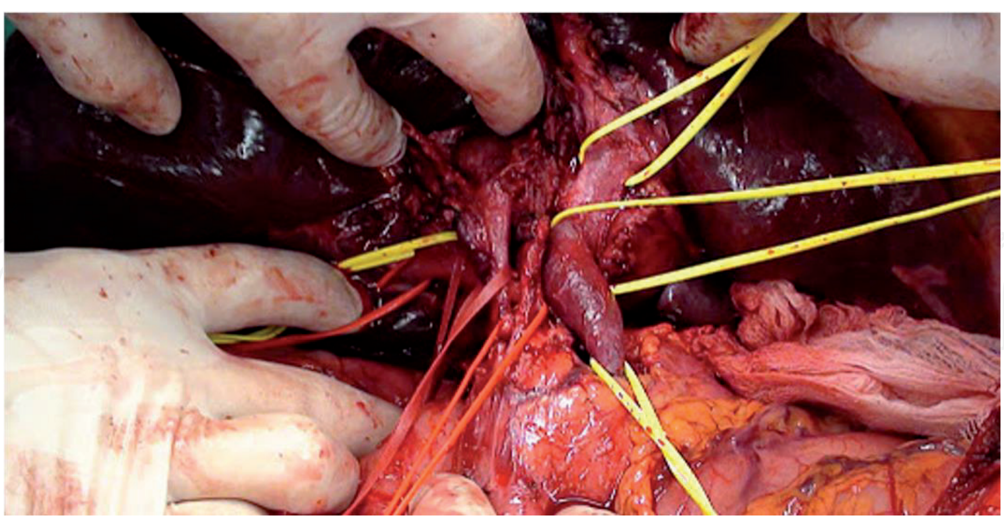

Figure 3.
Hilar dissection.

Anatomic and non-anatomic hepatectomies, wedge resections and liver ablations are routinely performed for the treatment of HCC from our team. Anatomic resections are selected in patients with unilobular disease and adequate liver function. Major hepatectomies include right and left hepatectomies, as well as extended right and extended left hepatectomies or trisectionectomies. Non-anatomic resections and liver ablation can be performed for smaller lesions, multilobular disease, in patients with previous hepatic resection (recurrence) or in cases with severely impaired liver function. Parenchymal sparing is crucial for maintaining adequate liver remnant post hepatectomy for these patients. In addition, vascular reconstructions in cases with vascular infiltration is possible in specific cases, as ex-vivo hepatectomy with auto-transplantation in cases of locally advanced/unresectable disease.

Figure 4.
Dissection of segmental branches.

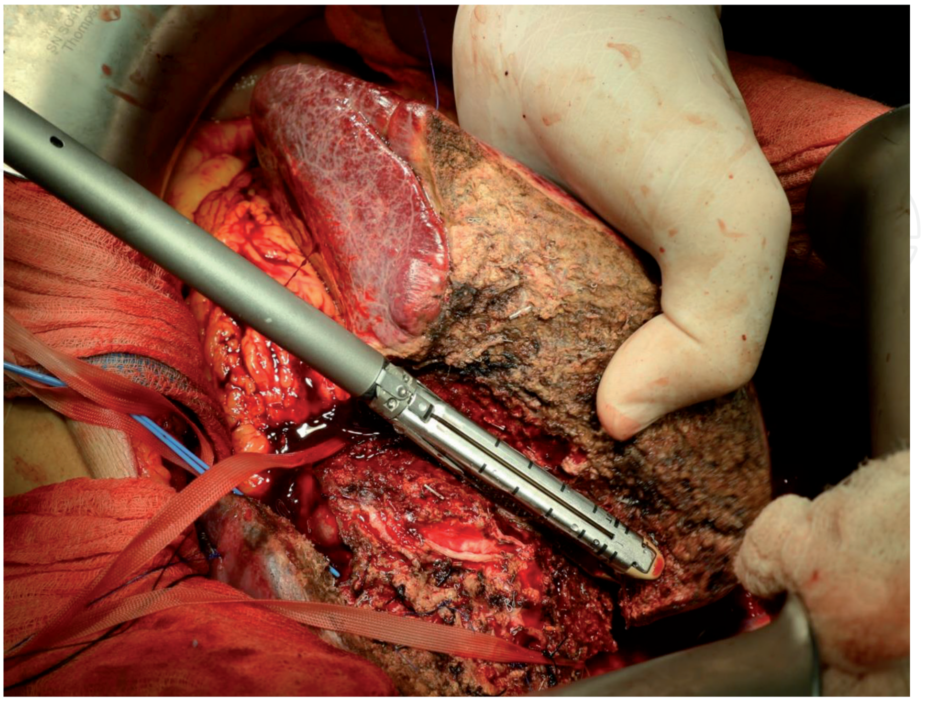

Figure 5.
Transection with vascular stapler.

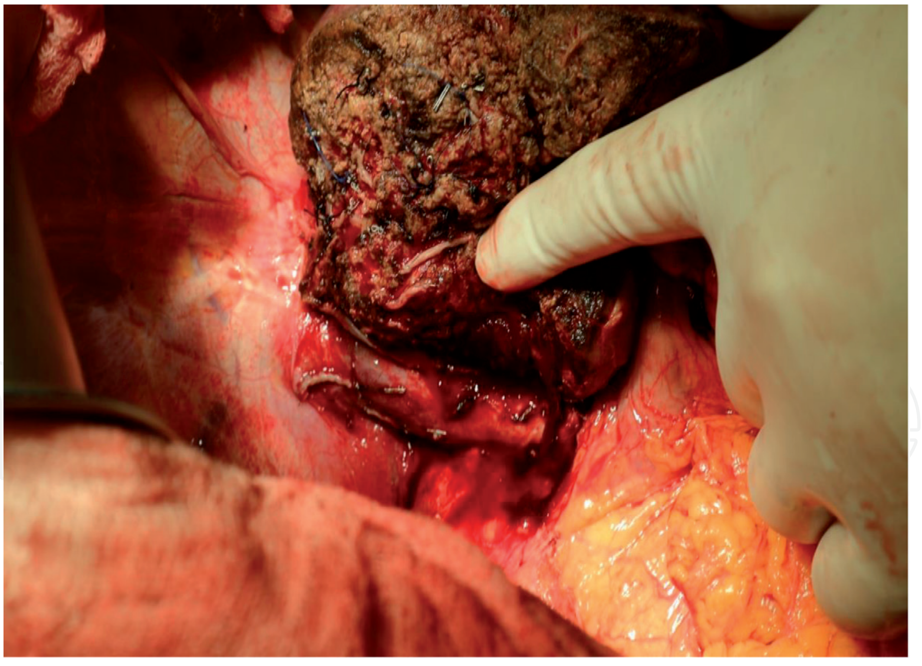

Figure 6.
Remaining liver parenchyma post right hepatectomy.

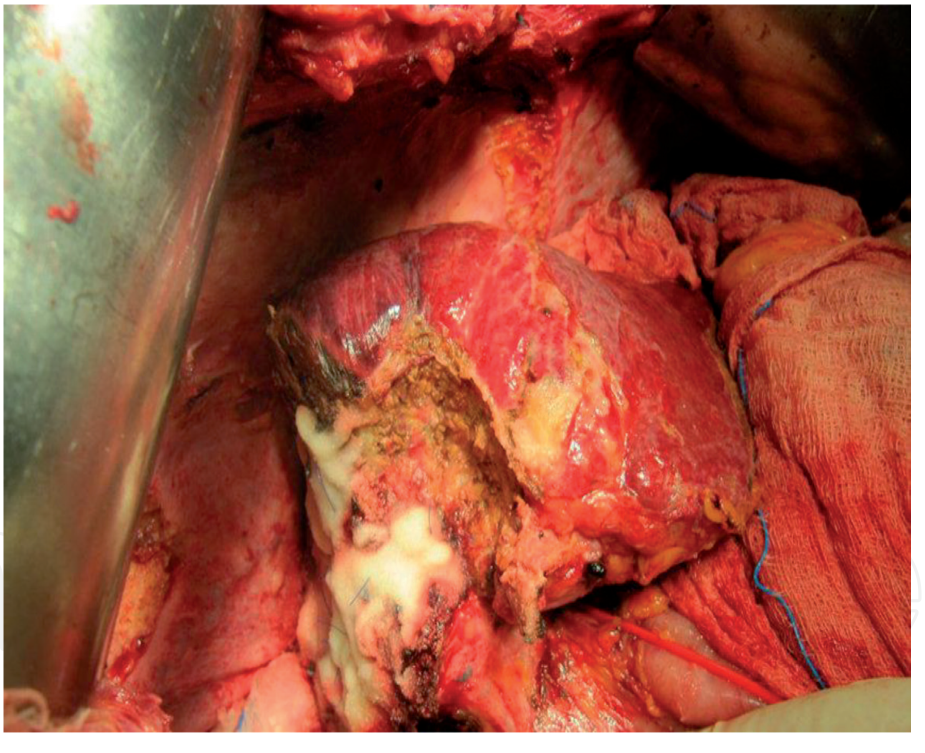

Figure 7.
Use of hemostatic-fibrin glue and final inspection.

9. Results

Between January 1st 2010 and January 1st 2021, more than n = 300 consecutive hepatectomies were performed in three referral hepatobiliary centers in Greece, from affiliated surgeons. Patients included in this study was treated for hepatocellular carcinoma and were treated with curative intent (hepatectomy). Adult patients that underwent elective operations were enrolled. All emergency operations or operations for other liver malignancies were excluded.

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N = 170 patients underwent liver resection for HCC during the study period. Mean age was 75 years (Range: 20–85). There were 115 males and 55 female patients. Etiology of liver disease was liver cirrhosis in most cases, due to alcoholic liver disease (ALD) (23.5%), hepatitis B (HBV) infection (42.35%), hepatitis C (HBC) infection (17.64%) and hepatic steatosis (16.4%). Most of the patients (n = 99, 55%) were BCLC-A patients, while n = 71 (45%) patients were BCLC-B or BCLC-C staged. N = 89 patients (52.35%) passed away during the follow-up. Post-operative complications according to Clavien-Dindo classification, were grade I in 54.66%, grade II in 24% and III-IV in 17.33% of the cases, respectively. Thirty and 90-day mortality rates were 1.13%. Mean length of hospital stay was 17.5 days. Mean OS was 46.66 months, while mean PFS was 31.56 months. OS figures for 1, 3 and 5 years was 87.14%, 64% and 42% respectively.

This data indicates that liver resection for HCC with utilization of the combined technique of saline-linked radiofrequency ablation and ultrasonic aspiration, is safe and feasible, leading towards bloodless liver resection without the use of vascular occlusion, ensuring that surgical treatment for HCC becomes comparatively safer (**Figure 8**).

Figure 8.
Right hepatectomy for HCC in a cirrhotic patient.

9.1 Minimally invasive liver resection

Minimally invasive liver resection is on the rise. However, the majority of performed operations are minor or limited resections in highly selected patients, from experienced hepato-biliary surgeons. The first laparoscopic liver resection was reported in 1991 [40], was referred to excision of peripheral hepatic lesions. Anatomic resections such as left lateral hepatectomy were followed thereafter [41]. The first series of laparoscopic hepatectomies were published in 1998 by Hüscher et al. [42] using totally laparoscopic and hand-assisted (hybrid) approach for right-sided liver resections.

Although it has several theoretical advantages, only a small percentage of liver resections are performed by minimally invasive surgery. A French national database study, published in 2014, presented that only 15% of liver resections were performed through minimally invasive approach [43].

Minor laparoscopic resections in anterolateral segments, as well as left lateral sectionectomy are considered the gold-standard approach in the hands of experts nowadays [44]. On the other hand, excision of bilateral lesions or lesions in postero-superior segments or in central locations of the liver (segments 1, 4a, 7, and 8), and mostly major hepatectomies are still considered rather challenging. Another key factor is the learning curve for minimally invasive liver resection, that can reach up to 75 operations [45].

Robot-assisted surgery has been gradually adopted as an alternative to laparoscopy, mainly in complex and major liver resections [46]. Despite all the potential advantages, most of the available evidence present no superiority of robotic assisted comparing to laparoscopic liver resections [47].

10. Conclusion

Hepatocellular Carcinoma (HCC) is the most frequent primary liver tumor. Well-established risk factors include chronic hepatitis B and C, non-alcoholic liver cirrhosis and liver steatosis amongst others, leading to impaired liver function in most cases. Surveillance programs and multi-disciplinary team approach aim to early diagnosis and effective therapy. Liver resection is the mainstay of treatment for HCC. All efforts are made towards bloodless hepatectomies, with adoption of newer techniques and evolvement of existing approaches. Laparoscopic or robotic liver resection can offer all the advantages of minimally invasive surgery in the hands of experts and for specific group of patients. Our technique of liver resection for HCC consists of saline-linked radiofrequency ablation and ultrasonic aspiration, is safe and feasible, leading towards bloodless liver resection without the use of vascular occlusion, ensuring that surgical treatment for HCC becomes comparatively safer in specialized hepatobiliary cancer centers.

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