EDITORIAL

The Journey of Radiofrequency-Assisted Liver Resection


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Conflict of interest:

Nagy Habib is a shareholder and director of EMcision Limited, which has developed the Habib 4X, one of the devices cited in this article not manufactured or currently marketed by this company

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Due to its high propensity for significant bleeding, the liver has historically been considered a treacherous organ on which to carry out surgery. The first patient reported to have undergone liver resection by Dr A Lius in Italy in 1886 died 6 hours post-operatively due to bleeding. In 1957, Claude Couinaud, a French surgeon who was also a dedicated liver anatomist, named the liver segments in a concentric way from segment 1 to segment 8 based on central Paris arrondissements[1]. Whether this is true or just an appealing myth, Couinaud was the first one to describe the segmental anatomy of the liver and introduced the concept of modern liver surgery based on the functional and surgical anatomy of the liver[2]. Only a few decades later, the “anatomical approach” for liver resection was translated into practice by Henri Bismuth, when he applied the knowledge of liver segmental anatomy to the liver resection technique to avoid complications, in particular uncontrolled hemorrhage, when performing non-anatomical liver resection[3].

The parenchymal transection phase of liver resection has always been a critical step. Several techniques to reduce intraoperative bleeding and liver-related complications have been developed, including inflow control (Pringle’s maneuver)[4], Makuuchi’s intermittent hemihepatic inflow occlusion[5] and other selective inflow clamping techniques[6], Glissonean pedicle approach[7], Belghiti’s technique for hepatic vein occlusion[8], total vascular exclusion[9], and the use of low central venous pressure during surgery[10].
After Bismuth, anatomical liver resection gained popularity in view of better outcomes, reduced blood loss and benefits of liver parenchyma preservation. Subsequently, with improvement in intraoperative ultrasound and surgical technique, segmental and subsegmental resections became the gold standard for liver resection, particularly for hepatocellular carcinoma[11-13].

For colorectal cancer liver metastases, the introduction of more effective chemotherapeutic agents, the expansion of criteria for resectability, the introduction of volume augmentation techniques (portal vein embolization, two-stage hepatectomies), the combination of resection with ablation, and the use of neoadjuvant chemotherapy to decrease tumour volume have all contributed to a significant increase in the number of patients with secondary liver tumors undergoing surgery[14]. In these patients, non-anatomical, parenchymal-sparing resection is now considered a comparable technique to anatomical resection with achievement of similar oncological outcomes[15].

Energy-based devices generate mechanic or electric energy to allow transection of the liver parenchyma and/or sealing of blood vessels and bile ducts during liver resection[16]. Different devices have been developed but no consensus exits in regards to standard technique for transection and hemostasis during liver resection. Some devices work as precoagulators (radiofrequency or microwave ablation devices); others work as sealing devices (bipolar forces, Ligasure, Enseal or Thunderbeat), whilst other (Ultracision or Cavitron Ultrasonic Surgical Aspirator - CUSA) works as ultrasonic shear or dissector.
Back in 2002, Weber et al. introduced a new technique for liver resection where radiofrequency energy was applied to allow precoagulation of the liver parenchyma before transection[17]. This technique has been improved with the use of a bipolar device (Habib™4X) that releases controlled radiofrequency energy to allow major hepatectomies as well as minor and non-anatomical resections with minimal blood loss, reduced need for blood transfusion and low morbidity and mortality rates[18, 19]. Since then, radiofrequency ablation applied with monopolar or bipolar devices has been used to minimize blood loss during open and laparoscopic liver surgery, reducing the need for vascular control, and facilitating parenchyma-sparing liver resection[20-22]. Our series of RFA-assisted liver resections between 2001 and 2010 consisted of 604 consecutive patients of whom 206 underwent major hepatectomy. Median intraoperative blood loss was 155mls with a 12.6% transfusion rate. There were no reported incidence of bleeding from the resection margin and morbidity was 23.5% with a mortality of 1.8%[21]. This series has since been updated to include all 857 consecutive patients operated on until 2015 illustrating a median blood loss of 130mls, 4.3% incidence of bile leak and a 30-day mortality of 1.5% [unpublished data].

Microwave energy has also been used as precoagulation method in liver surgery [23-25] and similarly causes coagulative necrosis of the liver parenchyma, but can potentially achieve a larger coagulation volume in a shorter time in comparison with radiofrequency ablation, although results seem comparable[26, 27].

There is evidence that perioperative morbidity is a strong predictor and possible cause of adverse disease-specific survival[28]. In particular, blood
loss and the need for blood transfusion are well-known factors influencing perioperative and long-term results, and the need for blood transfusion correlates better with outcomes than the estimation of blood loss[29-33].

It has been shown that radiofrequency ablation can reduce intraoperative bleeding and the need for blood transfusion in liver surgery[34]. Moreover, radiofrequency-assisted liver resection achieves excellent results in cirrhotic patients with shorter operative time, reduced blood loss and blood transfusion rate in comparison with the clamp-crush technique, and there is an association with improved survival particularly for large volume hepatocellular carcinoma[35-39].

The motivation behind the Habib 4x was indeed to reduce blood loss, to minimize the need for blood transfusion as well as the need for intensive care admission post liver resection. However, whilst reducing blood transfusion could be an indirect way of improving long-term survival in patients undergoing liver resection for cancer, there is now an emerging evidence-base that radiofrequency ablation could directly improve survival and reduce tumor recurrence by its effect on the immune system.

It has been demonstrated that radiofrequency ablation can stimulate local antitumor immunity as well as a systemic response with immunomodulatory effects through an increase in the number of tumor-specific CD8+ effector T cells[40, 41]. The theory being that the tissue left in situ following RFA of a tumour is a source of tumour antigen presentation. The antigens are taken up by local dendritic cells and presented to T lymphocytes in tumour draining lymph nodes, causing a direct expansion of tumour-specific CD8+ effector T cells. Moreover, it has been shown that radiofrequency ablation could produce
an abscopal effect with regression of distant metastases after ablation of the primary tumor[42] and pre-operative tumour ablation prior to surgery could improve survival by boosting the immune system against the tumor[43]. Radiofrequency ablation produces coagulative necrosis of the tissue that is targeted but also induces changes in the tissue surrounding the ablated area with increased sensitivity to chemotherapy and the development of antitumor antigen-specific immunity[44]. Improved outcomes of patients undergoing radiofrequency-assisted liver resection could be due to the systemic and local immunomodulatory effect of radiofrequency[45], however, the T cell-dependent antitumor immune response generated by RFA does not appear to be enough on its own to eradicate the cancer completely. The clinical outcomes for RF-assisted liver resection led to the development of a novel monopolar catheter for coagulation and ablation (Habib EUS RFA, EMcision Ltd., London, UK), deployed through an echoendoscope channel under ultrasound guidance. For suitable lesions in the pancreas or liver tumour ablation can be deployed via interventional endoscopy, thereby limiting the morbidity associated with surgical interventions for some patient groups. A multi-center pilot study of ablation of pancreatic lesions found the intervention to be well tolerated with a good safety profile and a response rate ranging from complete resolution to 50% reduction in size[46]. Improved outcomes have been shown also when radiofrequency ablation is applied percutaneously or during surgery without resection, with significant long-term survival for hepatocellular carcinoma, colorectal liver metastases, malignant biliary obstruction and even pancreatic cancer[47-50].
In recent years, major breakthroughs in immunological understanding and drug development, such as checkpoint inhibitors, have improved tumor management, with promising results also in the treatment of hepatocellular carcinoma, where chemotherapeutic options are still very limited[51]. In a recent trial by Duffy et al., 2017, activation of the immune system through checkpoint inhibitors and accumulation of intratumoral CD8+ T cells following radiofrequency ablation demonstrated synergism for the combined use of the checkpoint inhibitor tremelimumab and radiofrequency ablation in hepatocellular carcinomas [52]. Furthermore, recent studies have shown that this synergism of radiofrequency energy and checkpoint inhibitors could have a beneficial effect on long-term survival[43, 53-55], although these promising results need further confirmation through prospective trials. It may be that in the next few decades radiofrequency ablation and checkpoint inhibitors could be used initially as vaccine before surgery for liver cancer to further improve survival.

Liver surgery has come a long way over the past 70 years. The mortality rate from major liver resection is now around 1% in specialized centers and indications for surgery are constantly expanding. Further focus is being placed on minimally invasive approaches to decrease morbidity and postoperative pain and allow for faster discharge from hospital and earlier return to work following major liver resection. Our understanding of primary and secondary liver tumour carcinogenesis as well as the associated tumour microenvironment is allowing for more innovative treatment modalities, such as the combination of immunotherapy with radiofrequency ablation, to
complement the role of surgery and hopefully significantly improve cancer survival in years to come.
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