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Special article

Sutureless hepatic transection using a new radiofrequency assisted device. Theoretical model, experimental study and clinic trial

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A B S T R A C T

The ideal instrument for performing hepatic transection should combine safe and rapid haemostasis in a single tool. We present a new multidisciplinary investigation designed to develop a hepatic transection device assisted by radiofrequency (RF); the investigation included: a computerised theoretical model, and experimental study and a clinical trial of this device. The theoretic modelling was performed by computer, based on the Finite Elements Method (FEM), with the objective of studying the distribution of electrical energy and temperature in the tissue, and to assess the effect of the characteristics of the instrument. The experimental study, based on an in vivo porcine model, suggested that the new instrument would allow the transection velocity of the hepatic parenchyma to be increased with lower bleeding per transection area compared with other techniques extensively used in liver surgery. These data should enable the first phase of clinical trial to be conducted, with preliminary results that suggest that the new device is safe and effective.

Transección hepática sin suturas mediante un nuevo instrumento asistido por radiofrecuencia. Modelado teórico, estudio experimental y ensayo clínico

Palabras clave:
Instrumentos de transección hepática
Radiofrecuencia
Modelado por computador
Estudio experimental y ensayo clínico

R E S U M E N

El instrumento ideal para realizar la transección hepática debería aunar en una sola herramienta hemostasia segura y rápida. Presentamos nuestra investigación multidisciplinar encaminada al desarrollo de un dispositivo de transección hepática asistido por radiofrecuencia (RF); la investigación incluye: modelado teórico por computador, estudio experimental y ensayo clínico de este dispositivo. El modelado teórico se realizó por computador basado en el Método de Elementos Finitos (MEF) con objeto de estudiar la distribución de energía eléctrica y temperatura en el tejido y valorar el efecto de las características del

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instrumento. El estudio experimental basado en un modelo in vivo porcino sugiere que el nuevo instrumento permitiría aumentar la velocidad de transección del parénquima hepático con una menor hemorragia por área de transección al compararlo con otras técnicas ampliamente extendidas en la cirugía hepática. Estos datos permitieron afrontar la realización de la primera fase de un ensayo clínico, cuyos resultados preliminares sugieren que el nuevo instrumento es seguro y eficaz. los derechos reservados.

Introduction

In recent years we have seen the proliferation of a number of devices for performing hepatic transection. This reflects two things: on the one hand, our concern about lowering the surgery-related morbidity and mortality which are directly linked, amongst other factors, to intraoperative bleeding and surgical time; and, on the other hand, the need for a single device which combines the advantages of other devices and avoids their disadvantages.

As far as the first aspect is concerned, nowadays there is solid evidence linking intraoperative bleeding and the need for transfusions with a high mortality rate,[1-3] postoperative complications, especially infection,[4-7] and an increase in the risk of tumour relapse.[8] Hepatic surgery units have adopted measures which aim to reduce this bleeding/transfusion needs and have thus progressively improved the results obtained following hepatectomy, achieving mortality rates of less than 5% in many cases.[6,9]

There are two types of transection devices[10]: those mainly used for dissection (e.g. the haemostatic clamps or ultrasonic dissector) and mainly used for haemostasis and coagulation (e.g. sutures, endo-staplers, sealers, etc.).[5,10-14] In the second group, devices which use radiofrequency (RF) as an energy source (e.g. Habib® or TissueLink®)[3,6,7,15-18] have been developed in recent years, which has meant that RF has gone from being an ablative-palliative to a resective-curative technique.

The aim of this article is to present our multidisciplinary research, including the design and manufacture of the device in question from the perspective of biomedical engineering, the experimental study in an animal model and, finally, the clinical trial aimed at assessing the new RF-assisted device's safety and effectiveness in hepatic transection.[19-21]

Development

The new Coolinside® device (Apeiron Medical, Valencia, Spain) is a hand-held device which simultaneously coagulates (using RF) and cuts (by means of a cold scalpel) the liver. This device and its manipulation for both laparotomic and laparoscopic techniques have been described in previous articles[19-23] (Figure 1). Coagulation is performed by a blunt-tip metallic electrode positioned at the distal edge, which is electrically connected to a Cosman CC-1 coagulator system (Radionics, Burlington, MA, USA) operating at a maximum power of 90W. The liver tissue is cut using a thin blade at the distal edge.

Inside it the active electrode has a closed hydraulic circuit containing saline solution at a temperature of 0 °C, which is propelled to the distal edge by a Radionics continuous perfusion pump (Burlington, MA, USA) at a speed of approximately 130 mL/min. The cold liquid keeps the surface of the tissue below 100 °C by refrigerating the active electrode. The feedback system for the warm saline solution means that it can never come into contact with the patient (as in the case of the Tissuelink® device).

The key to the performance of the device is in the fact that the depth of hepatic parenchymal transection is adapted to the coagulation effect achieved by the proximal edge of the active electrode, that part which first comes into contact with the tissue (Figure 1). In this way, every time the surgeon moves the device over the surface of the liver, the parenchyma is cut and coagulated simultaneously.

Theoretical modelling

Theoretical modelling has become widely accepted for assessing the electrical-thermal performance of electrodes

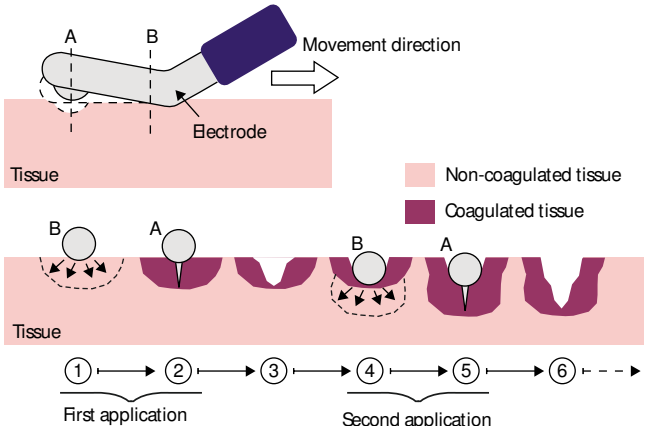

Figure 1 – Diagram to illustrate how the Coolinside® device works. Upper section of diagram: lateral view showing the distal section with the scalpel blade and coagulation with the proximal part active, as well as the direction in which it is advancing over the tissue. Lower section of diagram: transversal view of a fragment of tissue coagulated and resected in two sequential applications.

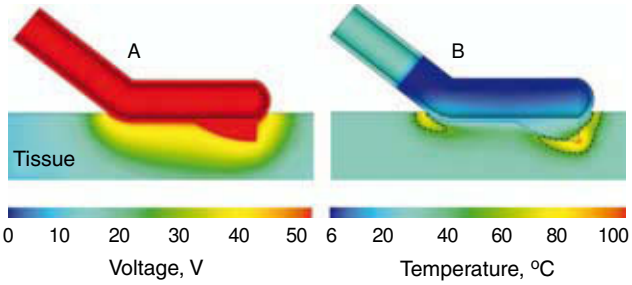

Figure 2 – Results of computer simulations of the theoretical model for the Coolinside® device. Distribution of electrical voltage A) and temperature B) in the tissue 4 secs. after application of 50V. The broken line represents the 55°C isotherm which serves as an estimator of the limit for thermal damage. Note the tendency for power to concentrate in the areas with the highest spatial voltage gradient (proximal area and tip of the blade). Theoretical modelling enables different geometrical designs for electrodes, blades, etc. to be readily evaluated.

and RF applicators on biological tissues. Tissue temperature is estimated by means of the Bioheat Equation, which includes tissue properties, density, specific heat and electrical and thermal conductivity values, as well as the heat loss as a result of continuous blood perfusion. In our case the theoretical model equations were calculated by the Finite Element Method (FEM), using the ANSYS commercial programme (Canonsburg, PA, USA).[19,22]

In this way, the density of the electrical current distribution in the tissue was estimated and, subsequently, the temperature distribution for different tissue, anatomical, electric power distribution protocol characteristics, etc. Figure 2 shows the results of a simulation, regarding temperature distribution in the tissue. The physical dimensions of the applicator were calculated based on tissue dimensions and the length of the device. Once the results of the theoretical study were obtained, the characteristics of the definitive prototype were adjusted for both laparotomic and laparoscopic surgery (Figure 3).

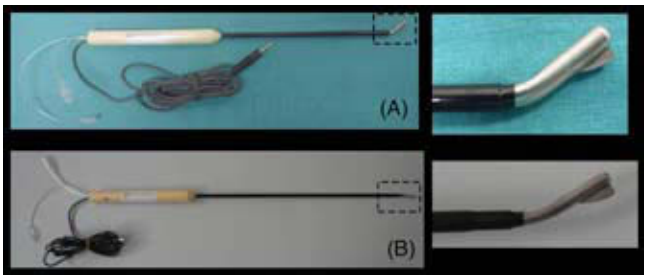

Figure 3 – Coolinside® hepatic transection device employed in experimental animal model studies. Models for open (A) and laparoscopic surgery (B).

In vivo study

After the *in vivo* study was approved by the local animal experimentation ethics committee, 24 hepatectomies were performed in 12 pigs. They were distributed as follows: 16 partial hepatectomies with the new hepatic transection device as the only transection method (eight by open surgery in four pigs and another eight using laparoscopy in another four animals), and the TissueLink® model DS 3.0 (Tissue-Link Medical, Doverm, NH, USA) was used for the other pigs.[19,21] In all cases, the efficiency of each device was assessed for transection and haemostasis, without the need to apply other devices (unless the bleeding lasted more than 2 min), using the following variables: transection time, bleeding volume, transection area, transection speed, bleeding adjusted to the area of transection and depth of the coagulated tissue.

During liver transection at least one or two veins with a diameter in excess of 5mm. were encountered. With TissueLink®, in 7 of the 8 transections stitches were required to achieve haemostasis. In contrast, with Coolinside® no stitches or other additional procedures were necessary to achieve complete haemostasis (without differences for the two types of surgery). In addition, as Table 1 shows, Coolinside® managed to increase transection speed by up to 30% compared to TissueLink®. Furthermore, the average bleeding incidence per transection area was nearly 7 times

Table 1 – Results of the in vivo study in an experimental animal model comparing the Coolinside® and Tissue-Link® devices. 24 hepatectomies were performed in 12 pigs, 8 for each technique

	Coolinside®		Tissue-Link®	P[a]
Variables	Open	Laparoscopic	Open	–
Transection time, min	12 (3)	13 (7)	21 (7)	.006
Bleeding, mL	70 (74)	26 (34)	527 (273)	.001
Transection area, cm^2	35 (7)	34 (11)	41 (8)	NS
Transection speed, cm^2/min	3 (0)	3 (1)	2 (1)	.002
Bleeding per transection area, mL/cm^2	2 (2)	1 (1)	13 (6)	.001
Depth of coagulated tissue, mm	6 (2)	9 (2)	3 (1)	.005

The differences in the variables were considered significant where $P<.05$.
NS indicates no significant difference.
[a]The measurements for each variable were only compared for the open procedure.

lower in the group in which Coolinside® was used in comparison with the TissueLink® group. All the animals tolerated the procedure well and were later sacrificed.

Technical modifications

After these initial experiences, some modifications were made to the accessories for the Coolinside®.[19] Firstly, a switchbox was designed to act as an interface between the RF generator and the device, in order to avoid the generator shutting down when tissue impedance exceeds a certain value, either as a result of delivering RF power into the tissue or simultaneously using other devices (for example TissueLink®), which is common in liver surgery.

To avoid problems with the tissue impedance range the switchbox also includes internal resistances, which balance and maintain the total impedance «recorded» by the RF generator within ranges which are appropriate for the generator, even in extreme short-circuit and open-circuit conditions. The switchbox also enables the Coolinside® to be operated by means of a pedal and not via the front panel of the RF generator.

Clinical trial

Given that the results of the *in vivo* study were satisfactory, we decided to conduct a clinical trial (registration number: AGEMED 312/08 EC), having first obtained the approval of the clinical trial ethics committee of the Hospital del Mar and the Spanish medicines and healthcare products agency (*AEMPS*).[23]

Briefly, the clinical trial consists of two phases: the first, known as the «safety phase», which included 8 patients and the second, known as the «efficacy phase», which includes 18 patients and is currently underway (which is why no data will be provided in this article). The inclusion criteria of the patients and data collection method are explained in detail in previous articles. With regard to the inclusion criteria, it should be emphasised that they were more stringent during the first phase and that, in view of the satisfactory results that were obtained, they were relaxed so that in the second phase, which is currently ongoing, we now include any type of hepatectomy using the new device.

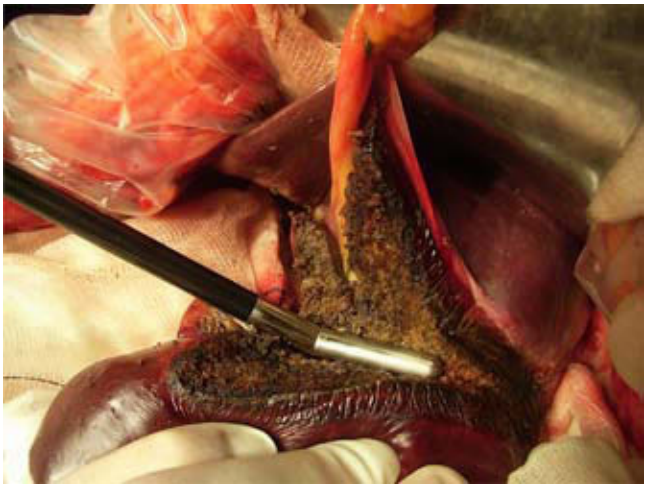

Figure 4 – Photo of Coolinside® transection during the clinical trial. The photo corresponds to a bisegmentectomy 2, 3 performed on the third patient in the series.

From September 2008 to May 2009, 11 hepatectomies, which included a total of 12 tumours in eight patients (5 males and 3 females) with an average age of 69.4 years (61-78 years), were performed with the Coolinside®. The average tumour diameter was 2.07 cm (range 0.8-6 cm). From all of them we collected a series of preoperative and intraoperative variables, primarily those we referred to for the *in vivo* study, and, finally, postoperative analytical and clinical variables (complications according to the Clavien severity scale[24] and mortality).

As far as surgery is concerned, we should mention that all the hepatectomies were performed entirely with this device (Figure 4), without any others being used (including ligatures or clips) or temporary vascular occlusion strategies (Pringle manoeuvre). The average resection time for each patient was 51 min (range 38-87 min) and the average transection speed was 1.28 cm^2/min. If we analyse the data for each hepatectomy, the average hepatic transection time was 39.9 min (range 13-65 min) and transection speed per cm^2 was 1.18 min (range: 0.49-1.73). In 4 patients some other additional surgical procedure was performed (Table 2). The average

Table 2 – Characteristics of surgery and postoperative outcome for the patients included in the clinical trial (Phase I)

Experience	Hepatic surgery	Additional surgery	Complications (Clavien)	Hospital stay, days
1	Limited resection	Stoma closure	Wound infection, I	9
2	2 limited resections	Ligature of the left portal vein	–	6
3	Bisegmentectomy 2-3	Anterior rectum resection + hysterectomy+partial cystectomy	Anastomotic dehiscence Re-intervention: Hartman (IIIb)	33
4	2 limited resections	–	–	6
5	Bisegmentectomy 2-3 and limited resection	–	–	6
6	Limited resection	–	Enterocolitis (II)	18
7	Limited resection	Hernia repair	Seroma (I)	4
8	Bisegmentectomy 6-7	–	–	4

intraoperative bleeding associated with hepatic resection was 42.5 mL (range 5-420 mL) and the average bleeding adjusted for transection area was 0.79 mL/cm^2 (range 0.05-7.37 mL). None of the eight patients required the transfusion of blood products during surgery or during the postoperative period.

With regard to surgical outcome and complications, none of them are directly related to the hepatic surgical procedure. In most cases these complications are related to the additional surgical procedures (Table 2). We should also point out that bile leak failed to occur in any of the patients included in the study. There were no fatalities.

Discussion

The deployment in recent years of new different devices for hepatic transection is merely a sign of an underlying problem: our concern about improving the results for this complex form of surgery, which has historically been linked to high morbidity and mortality.[10,11]

It is very important to reduce the complications which are potentially associated with hepatic surgery, especially now as the treatment strategy for hepatic metastases has changed, leading to an increase in this type of intervention. The percentage of patients requiring surgery for hepatic metastasis has doubled since the San Francisco conference consensus, increasing from 20%-25% to 58% in the latest series. This is due to the expansion of the criteria for resectability, in which "what is left behind" is taken into account rather than "what is removed", there being a tendency to perform more economical/conservative hepatic parenchymal surgery.

The expansion of the resectability criteria has substantially increased the number of non-anatomical resections, which are associated with greater intraoperative bleeding. Undoubtedly, intraoperative bleeding is one of the great challenges/fears of liver surgeons, given that it is associated with high short- and long-term morbidity and mortality and with lower disease-free survival.[1,2] To solve this problem, different devices have been developed, and all of them with certain advantages that are enhanced when they are used in combination, making this type of surgery labour-intensive.

Amongst the different hepatic transection devices, we would highlight those that use RF as an energy source (Habib®, Inline® or Tissuelink®). This has enabled intraoperative bleedings to be significantly reduced,[4-7,25-29] especially if they are combined with other devices (stitches or clips) to complete the haemostasis of the venous or portal branches. With regard to the creation of devices for liver transection, our group presents and describes a new technique that also uses RF as the energy source. It combines parenchymal transection and haemostasis functions in a single device, without requiring any additional method, not even temporary vascular occlusion.[19-23] The efficacy of the new device has been demonstrated in an animal model and optimised by theoretical modelling in order for it to be applied with good results in patients.

In the clinical trial presented here it has been demonstrated that bleeding adjusted to the transection area is lower (0.79 mL/cm^2, range: 0.05-7.37) than in the data presented by other groups in different studies conducted with devices which have been widely validated and used. However, as yet this assertion should be taken with caution, given that our research is a safety study and had no control group.

With regard to transection speed, we find ourselves in a similar situation. The available data indicates that the proposed device, employed in isolation, falls into the same speed range as other device combinations. In addition, it is more than likely that this speed can be increased as the procedure becomes more generalised, as was shown in the *in vivo* study.[19,20]

Furthermore, there were no bile leak complications in the first phase of the clinical trial. We would like to stress this finding, as it is a feared and relatively frequent complication in this type of surgery (up to 12% in some series[30-32]). There is no doubt that its absence in our series is related to the pre-coagulation of up to a depth of 5mm in the resection plane of the remaining liver and the subsequent sealing of the blood vessels and probably of bile conduits, owing to the histological similarity of the bile duct. However, we need to be cautious in interpreting this successful result, as it is probably also related to the number of patients and the proportion of resections which were performed (a greater number of limited resections than standard resections).

The potential advantages of Coolinside® technology seem evident: it provides us with a tool which enables us to reduce intraoperative bleeding and increase transection speed, given that this is a device which combines coagulation and transection capacity and it does not need to be combined with other devices (not even stitches or clips). Moreover, it is not necessary to perform vascular occlusion, parenchymal coagulation is homogeneous and, lastly, there is the possibility of using it in laparoscopic surgery. All this undoubtedly simplifies the technique but we must remember that the simplicity of the method does not diminish the importance of the surgeon's experience and skills.

However, alongside these advantages, there is also a series of evident limitations. As with other RF devices, tissue pre-coagulation can change structures so that it can be difficult to identify the main hepatic vessels or conduits.[33] Moreover, the amount of hepatic tissue that is sacrificed may be greater than in the case of other techniques, given that with this device the coagulated area may be up to 5 mm, which might limit but not contraindicate this technique in cirrhotic patients. Obviously, as with any other device using electricity as its energy source, precaution must be taken to avoid errors in the placement of dispersive electrodes. One final limitation is related to the clinical application of the device. The data available to date is limited to the safety study, which suggests that the Coolinside® device is safe for hepatic transection. However, its final utility will need to be contrasted, in comparative studies, against the tools which are in general use.

The results of this multidisciplinary study, which includes all the design and test phases of a device designed for hepatic transection, suggest that it is safe and it does not need to be used in combination with another device to achieve haemostasis. Although we have to wait until the efficacy

study is concluded, it seems to reduce blood loss and increase transection speed, compared with other devices which are currently on the market.

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Conflict of interest

Dr. F. Burdío and Dr. E. Berjano declare that they have a commercial stake in Apeiron Medical, a company with licence for patent application EP2145597A1, on which the Coolinside® device described in this article is based.

REFERENCES

1. Palavecino M, Kishi Y, Chun YS, Brown DL, Gottumukkala VN, Lichtiger B, et al. Two-surgeon technique of parenchymal transection contributes to reduced transfusion rate in patients undergoing major hepatectomy: analysis of 1,557 consecutive liver resections. Surgery. 2010;147:40-8.
2. Dixon E, Datta I, Sutherland FR, Vauthey JN. Blood loss in surgical oncology: neglected quality indicator? J Surg Oncol. 2009;99:508-12.
3. Geller DA, Tsung A, Maheshwari V, Rutstein LA, Fung JJ, Wallis Marsh J. Hepatic resection in 170 patients using saline-cooled radiofrequency coagulation. HPB (Oxford). 2005;7: 208-13.
4. Di Carlo I, Pulvirenti E, Toro A. Use of dissecting sealer may affect the early outcome in patients submitted to hepatic resection. HPB (Oxford). 2008;10:271-4.
5. Chiappa A, Bertani E, Biffi R, Zbar AP, Viale G, Pruneri G, et al. Effectiveness of LigaSure diathermy coagulation in liver surgery. Surg Technol Int. 2008;17:33-8.
6. Ayav A, Jiao LR, Habib NA. Bloodless liver resection using radiofrequency energy. Dig Surg. 2007;24:314-7.
7. Delis SG, Bakoyiannis A, Tassopoulos N, Athanasiou K, Madariaga J, Dervenis C. Radiofrequency-assisted liver resection. Surg Oncol. 2008;17:81-6.
8. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR, et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. Ann Surg. 2009;249:617-23.
9. Poon RT. Current role of laparoscopic surgery for liver malignancies. Surg Technol Int. 2007;16:73-81.
10. Gurusamy KS, Pamecha V, Sharma D, Davidson BR. Techniques for liver parenchymal transection in liver resection. Cochrane Database Syst Rev. 2009;CD006880.
11. Santoyo J, Suárez MA, Fernández Aguilar JL, Pérez-Daga JA, Sánchez-Pérez B, González-Sánchez A, et al. [Solid organ transection. Open and laparoscopic surgery]. Cir Esp. 2009;85(Suppl 1):40-4.
12. Schemmer P, Friess H, Dervenis C, Schmidt J, Weitz J, Uhl W, et al. The use of endo-GIA vascular staplers in liver surgery and their potential benefit: a review. Dig Surg. 2007;24: 300-5.
13. Schemmer P, Friess H, Hinz U, Mehrabi A, Kraus TW, Z'Graggen K, et al. Stapler hepatectomy is a safe disresection technique: analysis of 300 patients. World J Surg. 2006;30: 419-30.
14. Saiura A, Yamamoto J, Koga R, Sakamoto Y, Kokudo N, Seki M, et al. Usefulness of LigaSure for liver resection: analysis by randomized clinical trial. Am J Surg. 2006;192:41-5.
15. Ayav A, Jiao L, Dickinson R, Nicholls J, Milicevic M, Pellicci R, et al. Liver resection with a new multiprobe bipolar radiofrequency device. Arch Surg. 2008;143:396-401. Discussion 401.
16. Strasberg SM, Drebin JA, Linehan D. Use of a bipolar vessel-sealing device for parenchymal transection during liver surgery. J Gastrointest Surg. 2002;6:569-74.
17. Delis SG, Madariaga J, Bakoyiannis A, Dervenis C. Current role of bloodless liver resection. World J Gastroenterol. 2007;13:826-9.
18. Arita J, Hasegawa K, Kokudo N, Sano K, Sugawara Y, Makuuchi M. Randomized clinical trial of the effect of a saline-linked radiofrequency coagulator on blood loss during hepatic resection. Br J Surg. 2005;92:954-9.
19. Burdio F, Berjano EJ, Navarro A, Burdio JM, Grande L, González A, et al. Research and development of a new RF-assisted device for bloodless rapid transection of the liver: computational modeling and in vivo experiments. Biomed Eng Online. 2009;8:6.
20. Burdio F, Navarro A, Berjano E, Sousa R, Burdio JM, Guemes A, et al. A radiofrequency-assisted device for bloodless rapid transection of the liver: a comparative study in a pig liver model. Eur J Surg Oncol. 2008;34:599-605.
21. Navarro A, Burdio F, Berjano EJ, Guemes A, Sousa R, Rufas M, et al. Laparoscopic blood-saving liver resection using a new radiofrequency-assisted device: preliminary report of an in vivo study with pig liver. Surg Endosc. 2008;22:1384-91.
22. Berjano EJ. Theoretical modeling for radiofrequency ablation: state-of-the-art and challenges for the future. Biomed Eng Online. 2006;5:24.
23. Burdío F, Grande L, Berjano E, Martínez-Serrano MA, Poves I, Burdío JM, et al. A new "single-instrument" technique for parenchyma division and hemostasis in liver resection: A clinical feasibility study. Am J Surg. 2010 Sep 22. [Epub ahead of print].
24. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
25. Haghighi KS, Wang F, King J, Daniel S, Morris DL. In-line radiofrequency ablation to minimize blood loss in hepatic parenchymal transection. Am J Surg. 2005;190:43-7.
26. Hutchins R, Bertucci M. Experience with TissueLink–radiofrequency-assisted parenchymal division. Dig Surg. 2007;24:318-21.
27. Kargozaran H, Wildendorf S, Khatri VP. Radiofrequency-assisted hepatectomy using bipolar Inline multichannel radiofrequency device (ILMRD): report of initial clinical experience. Hepatogastroenterology. 2009;56:1496-500.
28. Pai M, Jiao LR, Khorsandi S, Canelo R, Spalding DR, Habib NA. Liver resection with bipolar radiofrequency device: Habibtrade mark 4X. HPB (Oxford). 2008;10:256-60.
29. Yao P, Chu F, Daniel S, Gunasegaram A, Yan T, Lindemann W, et al. A multicentre controlled study of the InLine

radiofrequency ablation device for liver transection. HPB (Oxford). 2007;9:267-71.
30. Vigano L, Ferrero A, Sgotto E, Tesoriere RL, Calgaro M, Capussotti L. Bile leak after hepatectomy: predictive factors of spontaneous healing. Am J Surg. 2008;196:195-200.
31. Reed DN, Vitale GC, Wrightson WR, Edwards M, McMasters K. Decreasing mortality of bile leaks after elective hepatic surgery. Am J Surg. 2003;185:316-8.
32. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer. 2006;94:982-99.
33. Lupo L, Gallerani A, Panzera P, Tandoi F, Di Palma G, Memeo V. Randomized clinical trial of radiofrequency-assisted versus clamp-crushing liver resection. Br J Surg. 2007;94: 287-91.