HBP SURGERY WEEK 2022

Review of Various Hemostatic Materials for Liver Resection

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Conflict of interest

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- Nothing to declare.

Mortality after liver resection in the history

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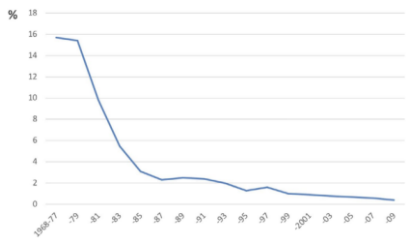

FIGURE 1 Variations in hepatectomy-related mortality, according to data from a nationwide follow-up study conducted by the Liver Cancer Study Group of Japan. In Japan, surgery-related mortality after liver cancer resection exceeded 15% in the 1970s, but decreased rapidly in the 1980s and reached a level as low as approximately 1% in the late 1990s[12]

Kokudo, Ann Gastroenterol Surg, 2020

Bleeding in the history of liver surgery

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Hepatic Lobectomy

MARTIN A. ADSON, MD, AND ROBERT R. JONES, MD, ROCHESTER, MINN. *Saturday, Nov 20, 1965*

TABLE 1.—*Total Removal of Right or Left Hepatic Lobe in Patients With Primary Hepatic Malignant Lesions*

Case	Age, yr; Sex	Type and Grade of Lesion	Resection: Extent	Resection: Amount, Gm	Transfusion, Ml	Days in Hospital	Follow-Up
1	58; M	Hepatoma, malignant, grade 2	Left total lobectomy + gallbladder	770	18,795 *	20	Living, no evidence of recurrence, 6 years postoperatively
2	53; F	Mucinous papillary cystadenocarcinoma, grade 2	Left total lobectomy	†	1,500	12	Living, no evidence of recurrence, 8 years postoperatively
3	61; F	Hepatoma, malignant, grade 2	Left total lobectomy	2,800	11,000 *	27	Died, 2½ years postoperatively; lung & bone metastases
4	62; F	Hepatoma, malignant, grade 1	Right total lobectomy + gallbladder	1,230	6,000	16	Living, no evidence of recurrence, 3½ yr postoperatively
5	15; M	Hepatoma, malignant, grade 2	Left total lobectomy + part of right hepatic duct	350	2,000	13	Living, no evidence of recurrence, 1¾ years postoperatively
6	24; F	Hepatoma, malignant, grade 4	Right total lobectomy + anterior medial segment of left lobe + gallbladder + part of diaphragm	1,300	13,500 *	15	Died, 2½ months postoperatively

* The anatomic factor responsible for the problem in hemostasis is described in the text.
† Weight unknown; surgical specimen was 20 cm in diameter.

Archives of Surgery, 1966

Bleeding in the history of liver surgery

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Hepatic Lobectomy

MARTIN A. ADSON, MD, AND ROBERT R. JONES, MD, ROCHESTER, MINN. *Saturday, Nov 20, 1965*

TABLE 2.—*Total Removal of Right or Left Hepatic Lobe in Patients With Benign or Metastatic Hepatic Lesions*

Case	Age, yr; Sex	Type and Grade of Lesion	Resection: Extent	Resection: Amount, Gm	Transfusion, Ml	Days in Hospital	Follow-Up
7	38; F	Benign, nonspecific, calcific abscess	Right total lobectomy + gallbladder	800	5,000	12	Living and well, 1 1/3 years postoperatively
8	64; M	Colonic carcinoma, grade 2 (1 year) *	Right total lobectomy + part of diaphragm + gallbladder	1,150	3,000	60	Died, 16 months postoperatively
9	46; F	Colonic carcinoma, grade 2 (2 year) *	Right total lobectomy + right adrenal + gallbladder	2,300	3,550	22	Died, 10 months postoperatively
10	29; M	Colonic carcinoma, grade 3 (synchronous)	Right total lobectomy + right colon + gallbladder	1,950	6,000		Died, 17 days postoperatively
11	60; M	Carcinoid, ileum (10 weeks) *	Right total lobectomy + gallbladder	1,000	16,000 †	39	Living and well, 7 months postoperatively; carcinoid syndrome relieved

* Interval since previous resection.
† The anatomic factor responsible for the problem in hemostasis is described in the text.

Archives of Surgery, 1966

Improved hemostasis with major hepatic resection in the current surgical era

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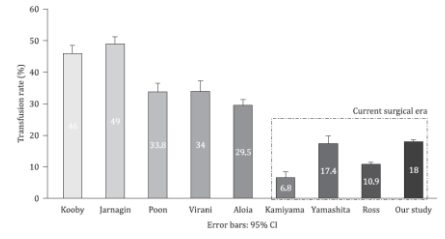

Mangieri, Hepatobiliary Pancreat Dis Int, 2020

Improved hemostasis with major hepatic resection in the current surgical era

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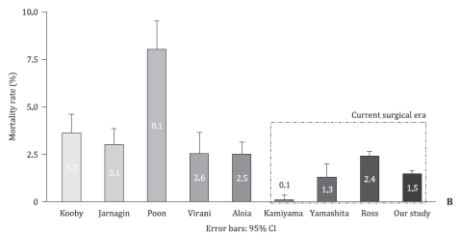

Mangieri, Hepatobiliary Pancreat Dis Int, 2020

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- Better visualization of surgical field
- Reduce surgical time

Proper Bleeding Control

- Improve surgical outcome
  - Reduce morbidity & mortality

- Fewer transfusion
- Reduce risk of infection
  - HIV, hepatitis, prions, etc
- Fewer immunological sequelae
  - Sensitization, transfusion reaction

How to reduce the bleeding during liver resection

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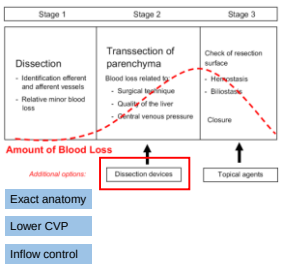

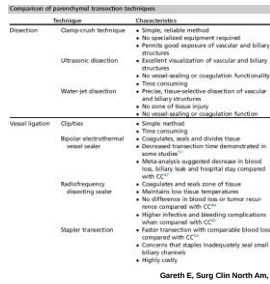

Gareth E, Surg Clin North Am, 2016

Fabrizio R, Hepatic surgery, 2012

How to reduce the bleeding during liver resection

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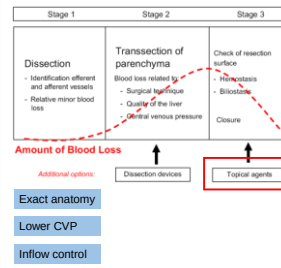

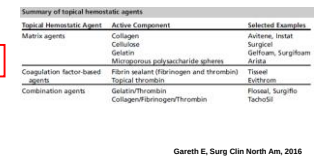

Gareth E, Surg Clin North Am, 2016

Fabrizio R, Hepatic surgery, 2012

What is hemostasis?

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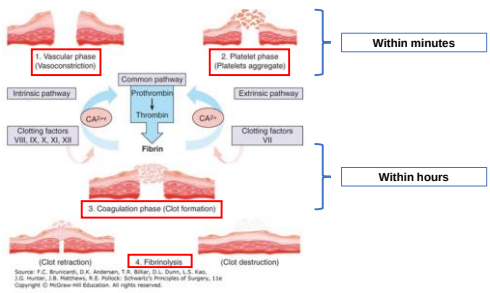

Schwartz's Principles of Surgery, 11th ed.

Coagulation cascade

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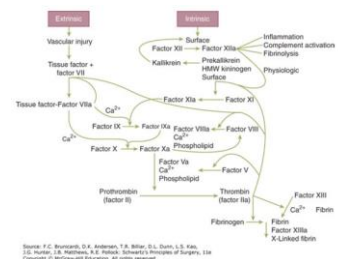

Schwartz's Principles of Surgery, 11th ed.

How to propagate the hemostasis

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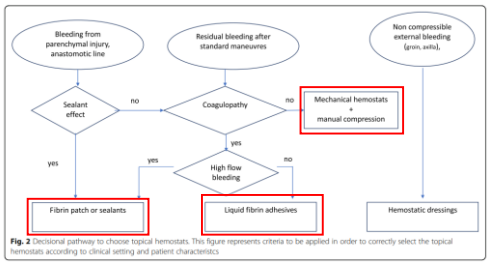

Fig. 2 Decisional pathway to choose topical hemostats. This figure represents criteria to be applied in order to correctly select the topical hemostats according to clinical setting and patient characteristcs

Osvaldo, BMC Surg, 2018

Mechanical hemostasis

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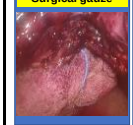
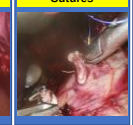
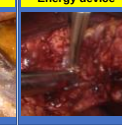
Surgical gauze	Sutures	Clips, clamps	Stapling	Energy device
				

Compression

Topical hemostats

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- Passvie mechanical
  - No coaguloation factors
- Active non-mechanical
  - Contain coagulation factors
- Active sealants (fibrin sealants)
  - Contain coagulation factors
- Passive sealants (synthetic and semi-synthetic glues and adhesives)
  - No coagulation factors

Topical hemostats

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- Passvie mechanical
  - Most effective for small amounts of bleeding
  - Do not contain any active biological substances to promte coagulation
  - Made from substaces such as cellulose, collagen and gelatin
  - Provide a mechanical barrier to blood and a matrix for platelet adhesion and aggregation
  - Risks: swelling of the material can cause nerve or tissue injury especially in closed areas such as the orbit, cranium or spine

Topical hemostats

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- Passvie mechanical

Surgicel: Cellulose sheet with bactericidal properties

TissuFleece and Lysostypt: Collagen fleece

Arista: Microporous polysaccharide powder

Surgifoam and Spongostan: Gelatin based in sponge or powder form

SurgiGuard: oxidized regenerated cellulose

Topical hemostats

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- Acitve non-mechanical
  - contain thrombin and are topically applied to the wound to promote coagulation
  - Effectiveness of thrombin can be enhanced by applying the product with an absorbable porcine gelatin in the form of a sponge or powder to which manual pressure can be applied
  - In the case of thrombin-coated granules (e.g. FloSeal), the product also acts as a site for platelet aggregation
  - Risks: immune-mediated coagulopathy. Thrombins should never be administered intramuscularly – associated with shock and massive intravascular thrombosis

Topical hemostats

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❖ Acitve non-mechanical

Floseal; Surgiflo: absorbable gelatin with thrombin

Recothrom: recombinant thrombin

Evithrom: human thrombin

Thrombin JMI: bovine thrombin

Topical hemostats

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❖ Acitve sealing (fibrin sealants)

- contain the active substances thrombin and fibrinogen which, when combined, form fibrin
- the fibrin cross links directly with exposed tissue collagen to anchor tissues and clots to wound surfaces
- Typically a flowable product that is topically applied to the bleeding site
- As they are flowable, these products do not offer immediate mechanical support
- Risks: excessively thick layers lead to poor healing and infection; air embolism, risk of swelling and coagulopathy

Topical hemostats

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❖ Acitve sealing (fibrin sealants)

Beriplast

Evicel

Tisseel

Greenplast

Topical hemostats

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❖ Passive hemostatic sealants/glues

- During surgery, in addition to blood loss, leakage of bile, lymph, urine, CSF and air may also occur. Synthetic or semi-synthetic glues can be used to help seal such leaks
- They create a physical seal and do not contain any clotting factors
- Products in this class do not clot blood

BioGlue: glutaraldehyde and bovine serum albumin

HemoPatch: collagen patch coated with NHS-PEG (also mechanical support)

Topical hemostats

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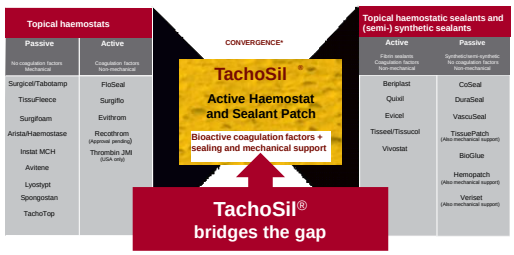

TachoSil®

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- Bleeding and fluid leaks remain technical challenges in surgery
- Insufficient haemostasis and tissue sealing may contribute to post-operative morbidity and mortality
- TachoSil® is indicated in adults for supportive treatment in surgery for improvement of haemostasis, to promote tissue sealing, and for suture support in vascular surgery where standard techniques are insufficient
- TachoSil® may help reduce the risk of bleeding complications while being cost-effective

TachoSil®

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Products	Active	Mechanical	Sealant
Surgicel, TissuFleece, Lysostypt, Arista, Instat MCH, Avitene, Surgifoam, Spongostan, Veriset		✔	
Floseal, Surgiflo, Evithrom, Recothrom, Thrombin JMI	✔		
Beriplast, Evicel, Tisseel, Quixil, Vivostat	✔		✔
Hemopatch		✔	✔
CoSeal, DuraSeal, VascuSeal, BioGlue			✔
TachoSil	✔	✔	✔

TachoSil® ticks every category

TachoSil® : physical characteristics

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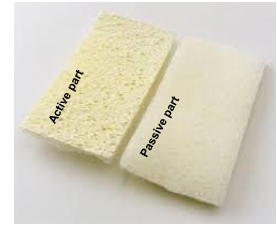
- TachoSil® combines the bioactive mechanism of action of human fibrinogen and thrombin for haemostasis and tissue sealing, with the mechanical support of a collagen patch
- TachoSil® is classified as a local hemostat



TachoSil® : physical characteristics - the passive part

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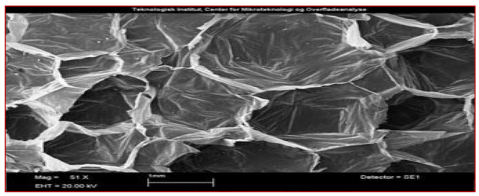
- The passive part of TachoSil® is a collagen patch composed of closed honeycomb-like cells with a weight of 1.3-2.0 mg/cm²



Scanning electron microscopy

TachoSil® : physical characteristics -the active part

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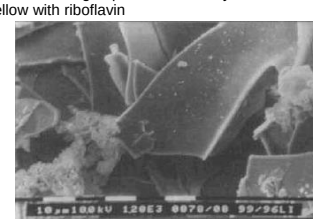
- The active side of the collagen patch is uniformly coated with coagulation factors and marked yellow with riboflavin



Scanning electron microscopy (x 1200)

TachoSil® : physical characteristics -unique properties create a strong seal

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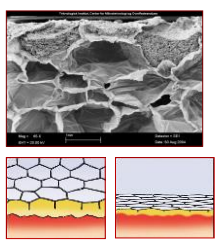

- Fibrinogen and thrombin is embedded in the open cells on the surface of the collagen sponge
- Upon contact with blood or other body fluids the coagul ation factors thrombin and fibrinogen are activated
- Activation of the coagulation factors and the collapse, n ot destruction, of the collagen cells conglutinate the Tac hoSil® patch with the tissue surface
- A seal is created between collagen patch and tissue

TachoSil® : physical characteristics -tensile capability

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- The proven pliability of TachoSil® ensures that it can be safely applied to moving organs such as heart, lungs and vessels — and stays in place while remaining intact

TachoSil® under stretch

TachoSil® : physical characteristics -adhesive strength testing

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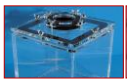

Pressure chamber

Porcine pleura with 10 mm hole punched out

Hole sealed with TachoSil®

Pressure applied

Pressure chamber with flanged porcine pleura with defect (10 mm diameter). Leak closed with 30 mm diameter TachoSil® patch. Pressure is applied via the pressure chamber until the patch lifts from the tissue. TachoSil® shows good adhesive strength – the maximum pressure tolerated was double that of TissuFleece (see next slide)

Proven: TachoSil® has adhesive strength to stay in place

TachoSil® : physical characteristics -adhesive strength comparisons

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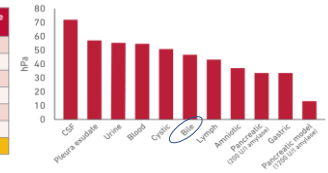
- The adhesive strength of TachoSil® is superior to other sealants.
- TachoSil® has been tested for adhesive strength in various body fluids.

	Mean maximum pressure tolerated (hPa)
Beriplast	8.2
Soft PGA Felt	14.4
Tachotop	19.2
TissuFleece E	30.7
TachoComb	59.7
TachoComb H	57.5
TachoSil (TachoComb S)	**61.4**



TachoSil® : physical characteristics -encourages natural wound healing

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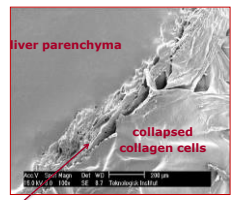
- Wound healing starts with haemostasis
- Blood cells (platelets) migrate to the wound/TachoSil® area
- Fibrin formed from fibrinogen provides a framework for the next stage of healing
- Blood cells secrete chemicals which attract collagen-secreting cells to the area
- Granulation tissue is formed from collagen, providing a scaffold for further tissue remodelling and scar formation



Scanning electron microscopy

fibrin clot
Deposition of a fibrin clot formed from the fibrinogen and thrombin in TachoSil® causes haemostasis and conglutination of the patch to the wound.

TachoSil® : physical characteristics -advantages

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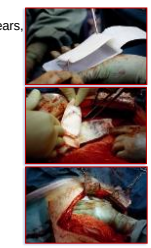
- TachoSil® can offer haemostasis in just three minutes[1,2]
- TachoSil® can be stored at room temperature for three years, ready to use when needed[3]
  - No thawing or defrosting
  - No mixing or other preparation before use
- TachoSil® can even be applied on moving organs[4]
  - TachoSil® can be cut to shape and applied wet or dry
  - TachoSil® moulds with the organ surface
- Can be applied to a bleeding/leaking surface3
  - Many other products need a dry surface to work
  - TachoSil® is not "washed away"



1. Molinaro C, Kjaergs HK, Bauernschmitt R et al. TachoSil surgical patch versus conventional haemostatic fleece material for intraoperative bleeding control in cardiac surgery: a randomised controlled trial. Eur J Cardio-thoracic Surg 2009; 36:708—714
2. Siemer S et al. Efficacy and safety of TachoSil as haemostatic treatment versus standard suturing in kidney tumour resection: a randomised prospective study. *Eur Urol* 2007;52:1156-63.
3. TachoSil® EMA SmPC
4. Carlton RT. Evaluation of biodegradable fleece-bound sealing: history, material science, and clinical application. In: Lewandrowski K, Wise DL, Trantolo DJ, Gresser JD, Yaszemski MJ, Altobelli DE, eds. Scientific and Clinical Applications. Marcel Dekker Inc, 2002: 587-650.

Evolution of TachoSil®

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- TachoComb® was developed in Germany and first launched in 1992
- TachoSil® was subsequently launched in 2004

TachoComb®	TachoComb H®	TachoSil®
Human fibrinogen	Human fibrinogen	Human fibrinogen
Bovine thrombin	Human thrombin	Human thrombin
Bovine aprotinin	Bovine aprotinin	Equine collagen
Equine collagen	Equine collagen	

No bovine components

TachoSil® in hepatic surgery

- rapid haemostasis during liver resection

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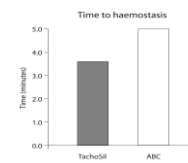
- The mean time to haemostasis was 1.4 minutes quicker with TachoSil® (3.6 min vs. 5 min, *p*=0.018).
- In some patients the difference was as great as 5 minutes in favour of TachoSil®.
- While TachoSil® application requires pressure and ABC does not, all resection procedures included application of pressure before other means of haemostasis.
- Compared with ABC, TachoSil® may offer a cost-saving, but this was not assessed in this study.



TachoSil can be recommended as a valuable tool for achieving standardised and fast haemostasis after liver resection.

Fischer L *et al.* 2011

TachoSil® in hepatic surgery
- reduction in postoperative complications

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Briceño J *et al.* A prospective study of the efficacy of clinical application of a new carrier-bound fibrin sealant after liver resection. Arch Surg 2010;145:482-88

- 115 patients undergoing conventional liver resection. Patients were randomised to have:
  - One or more TachoSil® patches applied to the raw surface of the liver (n=57)
  - Receive no haemostatic product (control group, n=58)
    - TachoSil® decreased the mean drainage volume (691.2 ml vs. 1124.7 ml in the control group) (p=0.007)
    - TachoSil® was also associated with a reduction in requirements for blood transfusion (7.0% of TachoSil® patients vs. 18.9% of control patients) (p=0.04)
    - There were fewer significant postoperative complications (such as bile leaks) in the TachoSil® group (8% of patients vs. 21% of control patients) (p=0.03)
    - The mean length of hospital stay was **9.6 days** for patients receiving TachoSil® vs. **12.6 days** for the control group (p=0.03) which has a positive impact on hospital budget

TachoSil® in hepatic surgery
- reduced bile leakage in split liver transplantation

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Toti L *et al.* Reduction in bile leaks following adult split liver transplant using a fibrin-collagen sponge: A pilot study. Digestive and Liver Disease 2010; 42: 205–209

- The study assessed the effect of treatment of the cut surface of the graft with TachoSil® (n=16) to seal vessels, compared with the use of fibrin glue (n=16)
- Post-operative bile leakage was less common in the TachoSil® group: 1 (6.25%) TachoSil® patient vs. 7 (43.75%) fibrin glue patients, p=0.03

Intra-operative view after application of TachoSil® to the cut liver surface

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Thank you for your kind attention.