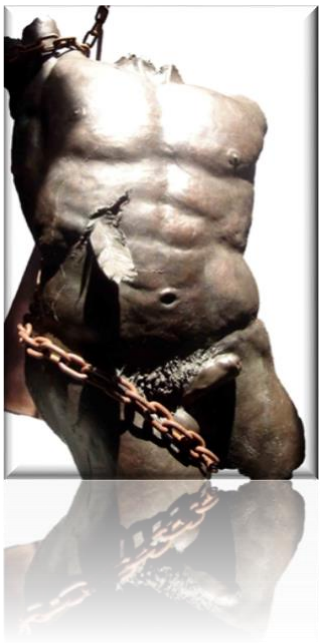
Prometheus: Prophylactic Mesh After OLtx for Hernia Reduction Study. A Multicenter Prospective, Consecutive Case Series Study, on the Use of a Bio-absorbable Mesh for Prevention of Incisional Hernia, in High Risk Patients, After Orthotopic Liver Transplantation.

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PROMETHEUS



"Homines ab immortalibus ignem petebant, neque in perpetuum servare sciebant; quem postea Prometheus in ferula detulit in terras, hominibus que monstravit quomodo cinere obrutum servarent.»

Gli uomini chiedevano il fuoco agli (dei) immortali, e tuttavia non lo sapevano conservare per sempre; successivamente Prometeo su un bastone portò questo sulla terra, e mostrò agli uomini come conservarlo coperto di cenere. (Igino, Prometeo, Fabulae, 144)

PROPHYLACTIC MESH after OLTx for HERNIA REDUCTION STUDY

A multicenter prospective, consecutive case series study, on the use of a bio-absorbable mesh for prevention of incisional hernia, in high risk patients, after orthotopic liver transplantation.

BACKGROUND

Incisional hernia (IH) is a possible complication of laparotomic surgery. Its incidence in low-risk patients after a midline laparotomy is nearly 9-20%, but that percentage increases to 30% in patients with multiple risk factors [**1**]. Risk factors for developing an IH after liver transplantation (LT) can be divided into:

- patient factors :
  - age >60, sex M, BMI equal to or higher than 25 kg/m², smoking, diabetes, IRC, moderate/severe ascites, MELD > 22, COPD,
- transplant/surgery related factors :
  - type of incision (Mercedes), delayed closure, wound infections, relaparotomy, ICU stay corticosteroids, mTOR-i

Transplanted patients are likely to present multiple risk factors, both patient and surgery related; for this reason, the incidence of incisional hernia in liver transplant (LT) moves from 5 to 46% [**2**].
In the EHS guidelines on the closure of abdominal wall incisions, prophylactic mesh augmentation for an elective midline laparotomy in a high-risk patient to reduce the risk of incisional hernia is suggested [**3-12**].
A RCT carried out in Germany, Austria and The Nederland among patients undergoing elective midline laparotomy and who had either an abdominal aortic aneurysm or obesity (PRIMA trial), showed that onlay prophylactic mesh, more than sublay, reduced from 30% to 13% the incidence of IH. PRIMA trial also advised a suture length-to-wound length ratio of 4:1 in all centers [**4**].
New bioabsorbable meshes seem to offer an appropriate tensile strengths and low recurrence rates while mirroring the decreased reactivity and infection rates associated with biologics.
An observational, prospective, multicenter study was conducted in 10 Italian clinical centers from May 2015 to February 2018 and in 15 Italian clinical centers from March 2018 to May 2019. The evaluation focused on patients with VHWG grade II–III who underwent primary ventral hernia repair or incisional hernia intervention with a follow-up of at least 18 months. The aim of the study was to assess the clinical outcomes and quality of life consequences of abdominal hernia repairs performed in Italy using Phasix and Phasix St meshes through the analysis of real-world data to support the choice of new generation biosynthetic meshes (Phasix is a macroporous, fully absorbable synthetic mesh that consists of co-knitted absorbable poly-4-hydroxybutyrate, while Phasix ST (Bard/Davol) is a composite mesh with additional polyglycolic acid fibers coated with a chemically modified sodium hyaluronate, carboxymethylcellulose, and polyethylene glycol-based hydrogel on the visceral surface, which allows intraperitoneal positioning). Conclusions of this study stated that Phasix meshes have proven to be suitable prostheses in preventing recurrence, with promising outcomes in terms of early and late complications and in improving patient quality of life [**5**].
No robust data are available about the use of Phasix mesh as prevention tool to reduce IH incidence. At present no data are available regarding the use of prophylactic mesh placement (PMP) in LT patients.
The only published ongoing protocol on this topic is the PRINC Trial. This is a monocentric randomized controlled trial comparing the incidence of IH between patients undergoing LT with or without prophylactic onlay biosynthetic mesh (Phasix) placement. The primary endpoint of the study is the comparison of the time to incisional hernia over a period of 12 months in 100 consecutive patiens. Secondary endpoint are: time to incisional hernia over a period of 24 months and rate of complications related to mesh placement [**2**].

Costs of incisional hernia

Scientific literature underlines that the average total cost for an IVHR (incisional ventral hernia repair) in France in 2011 was estimated to be 6,451€, ranging from 4,731€ in unemployed patients to 10,107€ in employed patients, whose indirect costs (5,376€) were slightly higher than the direct. Direct costs resulted from a multi-centric cost analysis done among a large panel of 51 French public hospitals, involving 3,239 IVHR. This study concludes that reducing the incidence of incisional hernia after abdominal surgery with 5 % for instance by implementation of the European Hernia Society Guidelines on closure of abdominal wall incisions, or maybe even by use of prophylactic mesh augmentation in high risk patients could result in a national cost savings of 4 million Euros [**6**].

A Pennsylvanian study upon 12,373 patients showed that the average total cost of admission index was \$27,065 ± \$51,805, whereas total readmission costs were \$34,489 ± \$60,901. There was no difference in index costs for patients experiencing hernia versus those without hernias (\$26,968 vs \$29,809, $P = 0.974$), average readmission costs were significantly higher for patients with hernia (\$32,807 vs \$57,267, $P < 0.001$) as was the overall combined cost of care (\$41,053 vs \$81,183, $P < 0.001$). Furthermore, patients experiencing hernia and subsequent recurrence requiring additional

surgery averaged $98,424 in combined costs of care ($P < 0.001$). This risk stratification model significantly predicted also increasing costs for high and extreme risk groups ($P < 0.001$). [**7**]

The cost-utility of prophylactic mesh, and specifically synthetic mesh, has recently been assessed by Fischer et al. in which the primary fascial suture repair was compared with PMA (Prosthetic Mesh Augmentation) in high-risk abdominal surgery patients. The results of the aforementioned study demonstrated an absolute reduction of hernia formation of 15% with prophylactic mesh and that PMA was less costly when the cost of treating all complications was considered; furthermore, prophylactic mesh continued to be the dominant strategy across a wide range of willingness-to-pay thresholds and robust Monte-Carlo sensitivity analyses. Specifically, in the base case scenario, PMA was cost-effective up to a mesh price of $3,700, assuming a willingness- to-pay of $50,000 per quality-adjusted life-year and a risk reduction of 15%, but the price of mesh could be as high $10,000 for higher willingness-to-pay and risk reductions. Overall, these findings strongly suggest that PMA has the potential for significant health care saving, particularly when used in high-risk patients [**8**].

STUDY DESIGN

Multicenter, prospective, consecutive case series study.

OBJECTIVE

The main purpose of the study is to determine whether a bio-absorbable mesh is effective and safe in the prevention of incisional hernia in high risk patients undergoing LT.

Primary endpoint:

- To evaluate the incidence of incisional hernias after LT in a consecutive series of patients that meet the inclusion criteria after conventional abdominal wall closure plus placement of a bio-absorbable mesh in an onlay position, at two years of follow-up.

Secondary endpoint:

- Incidence of IH in different type of incision subgroups
- Incidence of surgical site occurrences
    - Surgical site infection
    - Seroma
    - Evisceration (abdominal dehiscence)
    - Mesh complications
- Incidence of general complications
- Incidence of IH in different subset of patients undergoing immunosuppressants (steroids, mTORi)

MATERIALS & METHODS

- **multicenter prospective, consecutive case series study:** conventional closure technique (according to each center policy) + bio-absorbable mesh placed in an onlay position, with two-year-follow-up.

- **Approval by Local Ethics Committee**

- **Protocol, inclusion and exclusion criteria:**

Inclusion criteria: enrolled patients must be aged equal or >18 years, undergoing full liver, cadaveric OLTx for any indication (ACUTE LIVER FAILURE IN NON-CIRRHOTIC LIVER EXCLUDED); have good reperfusion of the transplanted liver after portal declamping; lactate < 10 mmol/L or

reduction after two consecutive samples 30 minutes after arterial declamping, achieved a good hemostasis, primary closure.

Have at least **3** of the following pre transplant **risk factors** for IH **(definition of high Risk Patients)**:

- **Age >60**
- **Sex M**
- **Obesity** (HR 1.74, 1.04 to 2.91) (16) (BMI equal to or higher than 30 kg/m², according WHO definition)
- **Smoker** (OR 3.93, 1.82 to 8.49) (14). An adult who has smoked at least 100 cigarettes in his or her lifetime, and who now smokes every day, according WHO definition.
- **Diabetes** (OR 6.68, 2.02 to 22.0) (14) as defined by Centers of Disease Control and Prevention):

Result	A1C Test	Fasting Blood Sugar Test	Glucose Tolerance Test	Random Blood Sugar Test
Diabetes	6.5% or above	126 mg/dL or above	200 mg/dL or above	200 mg/dL or above

- **IRC** according KDIGO definition: "CKD is defined as **abnormalities of kidney structure or function, present for >3 months, with implications for health**," and requires one of two criteria documented or inferred for >3 months: either GFR <60 ml/min/1.73 m2 or markers of kidney damage, including albuminuria.
- **MELD > 22** (16)
- **COPD** (HR 2.35, 1.44 to 3.83) (16): previous diagnosis of emphysema, chronic bronchitis, and chronic obstructive asthma. In pulmonary function testing, **a postbronchodilator FEV1/FVC ratio of <0.70** is commonly considered diagnostic for COPD according The Global Initiative for Chronic Obstructive Lung Disease (GOLD) system.
- **Moderate/Large ascites at time of transplant**. The International Ascites Club classifies the severity classification of ascites as follows: moderate ascites (grade 2): moderate abdominal distention, large ascites (grade 3): marked abdominal distention.
- **Sarcopenia** (if diagnosed with CT-scan or RM). The study of the muscular compartment at the level of the third lumbar vertebra (L3) by CT is the gold standard technique in the assessment of sarcopenia. (10) The sum of the areas of psoas, erector spinae, multifidus, quadratus lomborum, rectus of the abdomen, transverse and internal and external obliques are divided by the squared height of the patient and define the skeletal muscle index: SMI (Skeletal Muscle Index) = SMA (Skeletal Muscle Area) (cm²) / height (m²). Sarcopenia is defined by cut-off values below 41,6 cm²/m² for men and 32 cm²/m² for women. (11)

Exclusion criteria: retransplant, previous upper quadrants laparotomies, previous incisional hernia repair, umbilical hernia > 2cm in diameter, pre-Tx steroids treatment or immunosuppression, patient's rejection to participate.

PATIENTS ENROLLMENT

From the protocol start date and for the following 12 months, all the transplant candidates that meet the inclusion criteria will be enrolled at time of LT by any of the surgeons who belongs to the centers involved in this trial, and an informed consent will be obtained. During the one year enrolling period we aim to include 100 consecutive patients in the study.

INFORMED CONSENT

A detailed informed consent will be administered to all patients at enrollment. Moreover, the same detailed informed consent will be provided to the general practitioner.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY

Subjects will be on study for 24 months.
Treatment: day 0
Follow-up: 8 days, 30 days, 3, 6, 12, 18, 24 months
The total duration of the study is expected to be 3 years. One year for subjects recruitment and 24 months for final subjects follow-up.

SURGICAL PROCEDURES

The technique used for surgical incision and for abdominal wall closure will follow each participating center policy. A slowly absorbable material will be used for closure by all centers.
After conventional closure a bio-absorbable mesh will be placed in a onlay position (PHASIX - C. R. Bard, Inc/Davol Inc, Warwick, RI). The above mentioned meshes are currently available in the participating centers.
The surgeons will be specifically trained in using a prophylactic onlay mesh.
An overlapping of 3 cm must be obtained on every side of surgical incision.
Fixation methods allowed: interrupted long- term absorbable suture. Subcutaneous and skin closure following center practice. The operating surgeon can decide for the placement of a subcutaneous drain if necessary.

EVALUATION OF SAFETY

Perioperative variables will be recorded including:

- Demographics
    - Age
    - Sex
- Risk factors for IH
    - body mass index (BMI)
    - smoking habit: No/previous smoker/active smoker
    - COPD
    - MELD
    - ascites
    - hypertension

    - diabetes mellitus
    - umbilical hernia
    - sarcopenia
    - connective tissue disorders
    - cardiac disease
    - renal disease
    - anticoagulation
    - immunosuppression
    - oncologic
    - previous surgery

- diagnosis
- surgical technique (type of incision)
- surgical time
- Immunosuppressive protocol
- Postoperative complications (Clavien Dindo Classification)
    - surgical site infection (SSO, SSI, SSOPI)
    - wound seroma
    - hematoma
    - ileus
    - organ lesion or perforation
    - bleeding complications
- mesh infection
- general complications
- reoperation
- follow-up variables
    - Late SSI
    - Small bowel obstruction
    - Seroma
    - Persisting abdominal pain
    - Bulging
    - Abdominal wall hernia

The operative mortality will be defined as death within 30 days of operation.
These complications will be diagnosed and registered during hospital stay by the surgeons of the department.
To homogenize clinical criteria for the diagnosis of local complications, we will follow the next definitions:

- Incisional hernia will be diagnosed and classified following the definition included in the European Hernia Society Guideline (3-12): any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or visible at imaging.
- They will be also classified according to the above mentioned guideline.
- Surgical site infection as the presence of signs such as redness, pain, heat or swelling at the site of the incision or by the drainage of pus.
- Seroma as a mass or swelling in the wound caused by the localized accumulation of clear serum liquid without surgical site infection signs.
- Evisceration is defined as disruption of the abdominal wall during the postoperative period.
- Mesh infection is defined as chronic wound infection that required mesh removal to solve it.

Table 1 Nomenclature for complications in hernia surgery

From: SSI, SSO, SSE, SSOPI: the elusive language of complications in hernia surgery

Item	Earliest citation	Hernia specific	Definition (short)
Surgical site infection (SSI)	Centers for Disease Control and Prevention (CDC)	No	Infection occurring where the surgery took place and includes superficial, deep, and organ space infections
Surgical site occurrence (SSO)	Ventral Hernia Working Group (VHWG) Breuing et al. [2], updated with the present article	Yes	SSI, seroma, wound dehiscence, enterocutaneous fistula, wound cellulitis, non-healing incisional wound, fascial disruption, skin or soft tissue ischemia, skin or soft tissue necrosis, wound serous or purulent drainage, stitch abscess, seroma, hematoma, and infected or exposed mesh
Surgical site event (SSE)	Majumdar et al. [5]	Yes	SSIs, and clinically relevant SSOs, such as cellulitis, symptomatic seroma/hematoma, and suture granuloma occurring within 90 days of hernia repair
Surgical site occurrences requiring procedural interventions (SSOPI)	Baucom et al [4]	Yes	SSOs requiring a procedural intervention, defined as wound opening or debridement, suture excision, percutaneous drainage, or mesh removal

PATIENT FOLLOW-UP

An intention to treat analysis is planned.
Patient follow up will be carried out in the outpatient clinic at 30 DAYS, 3, 6, 12, 18 and 24 months by any surgeon involved in the trial.

Outcome measures

Incidence of IH: diagnosis of IH will be achieved by physical examination (or by ultrasound and/or Ct-scan only if confirmation is needed). During postoperative follow up all patients will perform abdominal wall ultrasound after 12 months from the surgical procedure, following the current clinical practice. At the end of the follow up (24 months), in order to overcome ultrasound limitations, all patients will undergo to CT scan with the patient straining to underline any wall defects, following the current clinical practice. All radiological images will be revised by a blinded radiologist with more than ten years of experience.

DATA COLLECTION

All data will be electronically collected in a online dedicated page of an already existing abdominal wall surgery database. All clinical data were anonymized and were collected according to the European General Data Protection Regulation (GDPR).

STATISTICAL ANALYSIS

During the one year enrolling period we aim to include 100 consecutive patients in the study.
The data from study group will be compared with an historical control group matched for clinical characteristics.
The description of the variables and the statistical analysis will be performed using the statistical package for the social sciences (SPSS) program. Quantitative variables will be expressed as mean and standard deviation (SD), and categorical variables as absolute numbers and percentages. The intention-to-treat analysis will include all patients, except those lost during the first 30 postoperative days. In the statistical analysis of the categorical variables, the Pearson chi-square test will be used. The appearance of incisional hernia during follow-up will be also analyzed with the Kaplan-Meier estimation method and the log-rank test. All data will be recorded in an online database.

PLANNED INTERIM ANALYSIS

An interim analysis for safety will be conducted by the main research once approximately 50% of patients have completed the study through the 1-year follow up visit. In addition, a committee will monitor serious adverse events on an ongoing basis throughout the study

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