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Influence of Titanium Coating on the Biocompatibility of a Heavyweight Polypropylene Mesh

An Animal Experimental Model

H. Scheidbach[a] A. Tannapfel[b] U. Schmidt[a] H. Lippert[a] F. Köckerling[c]

[a]Department of Surgery, Otto von Guericke University Magdeburg, Magdeburg, [b]Institute of Pathology, University of Leipzig, Leipzig, and [c]Department of Surgery and Center of Minimally Invasive Surgery, Hannover Hospital – Siloah, Hannover, Germany

Key Words
Polypropylene · Mesh · Titanium · Inflammation · Apoptosis

Abstract

Introduction: In light of the fact that, to date, no information is available about titanium relative to its application in prosthetic material employed for hernial repair, the aim of the present work was to evaluate the fundamental possibilities of titanium-coated polypropylene meshes. ***Materials and Methods:*** In experiments with animals, two groups, each containing 11 pigs, received either a heavyweight polypropylene mesh (Atrium®) or an identical but titanium-coated mesh (titanium-coated Atrium) implanted into the left groin using the totally endoscopic extraperitoneal patchplasty technique. ***Results:*** A significant difference in the shrinkage behavior between conventional Atrium and titanium-coated Atrium was found (14.9 vs. 8.8%, $p < 0.05$). Furthermore, the partial volume of the inflammatory infiltrate also proved to be smaller with the titanium-coated mesh (14.9 vs. 12.4%). In addition, Ki-67 expression was lower in the group implanted with titanium-coated mesh (21.0 vs. 15.0%). No difference was observed with regard to the apoptosis index (7.6 vs. 6.5). ***Conclusions:*** Heavyweight titanium-coated polypropylene meshes induce a less pronounced foreign body reaction in comparison with identical meshes with no titanium coating, which, since the amount of material implanted is identical, must be attributed solely to the titanium coating.

Introduction

Against the background of a dramatically escalating, and possibly uncritical, use of prosthetic materials in hernial repair, in particular with regard to inguinal hernias, pro and contra discussions have taken place in Germany in recent years, and this despite the fact that the percentage of hernial repairs using mesh is considerably lower than in such western industrialized countries as Great Britain, Sweden and The Netherlands, or the USA [1, 2]. A positive 'side effect' of this debate has been an enhanced awareness of prosthetic use in hernia surgery, coupled with an appeal to surgeons and the industry to undertake greater efforts to develop better biomaterials [3].

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H. Scheidbach, MD
Department of Surgery
Otto von Guericke University Magdeburg
Leipziger Strasse 44, DE–39120 Magdeburg (Germany)
Tel. +49 391 6715532, Fax +49 511 9272591, E-Mail scheidbach@t-online.de

Currently employed heavyweight polypropylene meshes are 'overdimensioned' and induce a severe chronic foreign body reaction over the long term. This in turn gives rise to scarring, which has a negative effect on the mechanics of the abdominal wall [1, 2, 4].

On the basis of positive long-term experience with titanium, in particular in the area of endoprostheses, an attempt has been made to utilize this material for prosthetic meshes in hernia surgery as well. Since, to date, no experience has been gained with the use of titanium in conjunction with prosthetic materials for hernial repair, the aim of the present study was to investigate the fundamental aspects of its potential application in this field, in terms of healing and chronic inflammatory reaction. For this purpose, a comparison was made of a heavyweight polypropylene mesh with and without a titanium coating, enabling any differences in behavior to be ascribed exclusively to the titanium coating.

Materials and Methods

In an animal experiment approved by the regional (Thuringian) authorities (Ref. No. 341.43-2684-04-08-01/99), a conventional heavyweight polypropylene mesh (Atrium®) was compared with an identical mesh provided with a titanium coating (titanium-coated Atrium). These meshes were implanted into two groups of 11 domestic pigs each.

To apply the titanium coating, a novel, so-called PACVD (plasma-activated chemical vapor deposition) technique, which was initially developed for the hardening of certain products, was employed. In this process, a titanium compound is vaporized and passed into a deposition chamber containing the material substrate. On the surface of the latter, chemical reactions take place, and the gaseous titanium compound is degraded, resulting in the deposition of the titanium on the substrate. The energy required to activate the surface reaction is not of a thermal form; rather, an electric field is employed to convert the gaseous to a plasma state, so that the reaction takes place at a temperature of only 45 °C. This method permits not only the inexpensive and homogenous coating of even geometrically complicated shapes, but also extremely thin coatings (here <30 nm) with a high adherence [5].

After removal from their sterile pack, the Atrium meshes were trimmed to the dimensions 9 × 6 cm. Titanium coating was performed by GfE Nürnberg, Germany. Thereafter they were re-sterilized and packaged.

After appropriate premedication and sedation, the animals were operated on under neuroleptanaesthesia. Implantation was carried out using a minimally invasive approach as in humans, in the form of a totally endoscopic extraperitoneal patchplasty (TEP). Following appropriate preparation, a patch was placed over the three potential hernia sites in the left groin [6].

After an in situ period of approximately 3 months, the experimental animals were killed with an overdose of trichloroethenediol. Prior to autopsy, a laparoscopic inspection and evaluation of the in situ implant was carried out, and the graft then removed en bloc together with adherent adjacent soft tissue structures. Thereafter, in order to assess the shrinkage of the patch, measurements were performed in the fresh, unfixed specimen taking care not to apply tension.

From each of the implants, five tissue specimens were obtained from predefined sites within 300 µm of the interface (tissue/mesh). Ten histological 5-µm-thick sections were then obtained and stained with hematoxylin and eosin. Thereafter, the partial volume of the inflammatory infiltrate (% PV) in the connective tissue was determined.

Also determined was Ki-67 (MIB-1) to evaluate the extent of cell proliferation, and the TUNEL/ISEL marker to establish the apoptotic cell death – expressed as the apoptotic index. Ki-67 and TUNEL staining was evaluated in six representative areas exhibiting the highest grade of inflammation. The positivity assessment was performed by calculating the number of positive cells using an integration grid under a microscope (Zeiss, Axioplan 2) (fig. 1). The results were presented as percentage of positive cells expressed as the median of all the values calculated [7, 8].

Both the graphic presentation and the statistical analysis were carried out with the aid of the software SPSS 7.0.1 for Windows (SPSS, Inc., Chicago, Ill., USA). All parameters were tested for significance with the aid of Welch's robust t-test for independent samples, with a p value of 0.05 being considered significant. In comparison to the classical t-test, this has the advantage of being applicable even when there is a non-normal distribution of values in the two groups.

The results are presented in the form of box plots, the median, 95% confidence interval, and extreme values (°: up to 2 × SD; *: up to 3 × SD). The box plot itself shows the interquartile range covering 50% of all values.

Table 1. Operative data (means and SDs)

	Conventional Atrium	Titanium Atrium
M:F ratio	3:8	1:10
Duration of operation, min	36.6 ± 13.9	31.4 ± 4.7
Initial weight, kg	25.1 ± 2.9	28.0 ± 2.2
Weight at sacrifice, kg	68.8 ± 8.6	90.0 ± 9.1
Increase in weight, %	274	321
In situ time, days	89.2 ± 1.0	102.7 ± 0.5

Results

In two groups of 11 domestic pigs each, a heavyweight polypropylene mesh (Atrium®) or a titanium-coated, but otherwise identical, heavyweight polypropylene mesh was implanted. In both groups the patch was placed by the use of the TEP approach, and both the operative procedure and the mesh-handling properties were unremarkable in each group (table 1).

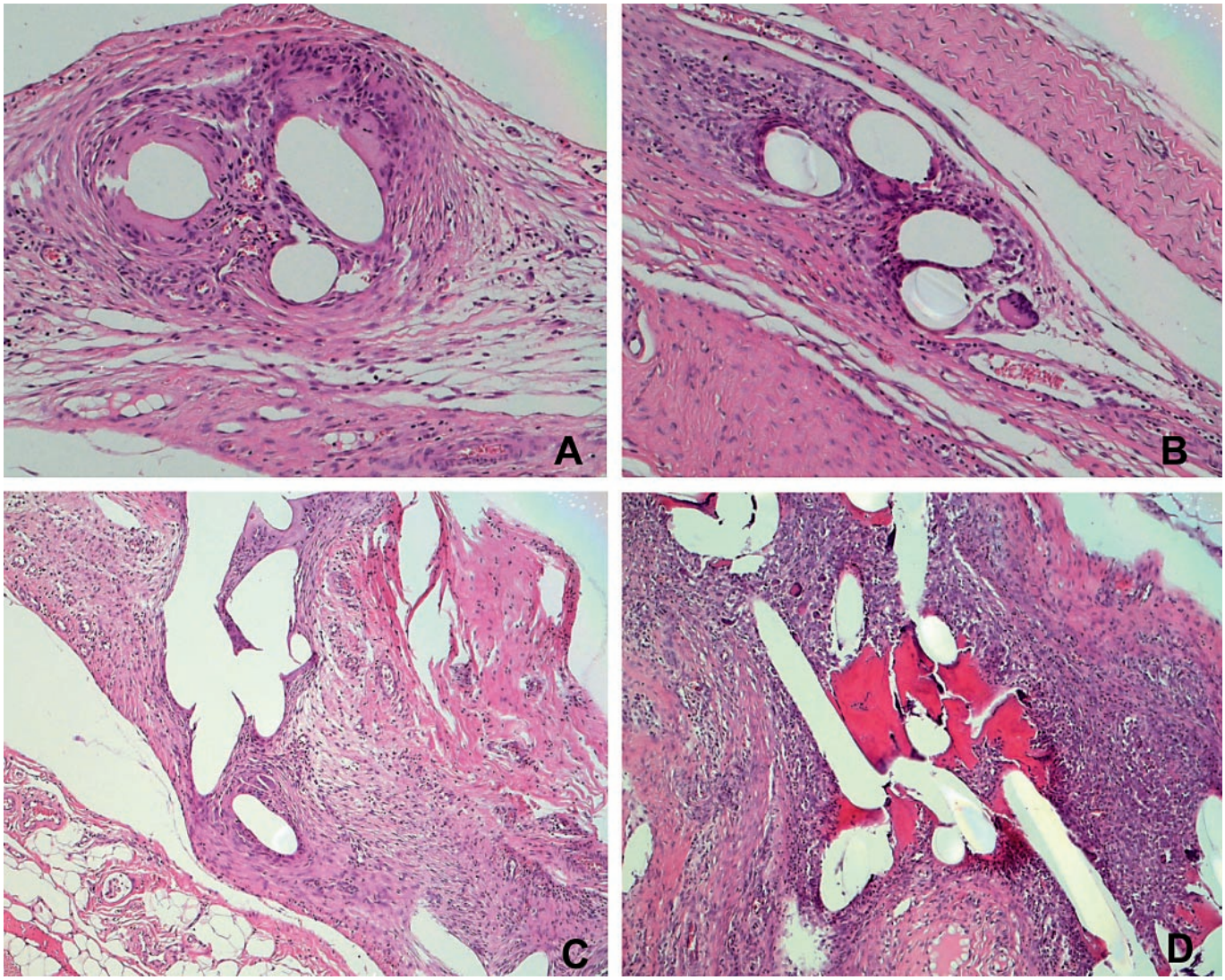
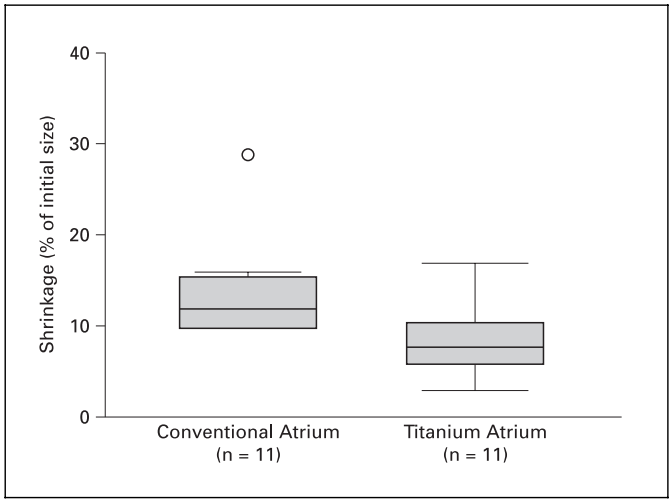


Fig. 1. **A**, **B** Titanium Atrium, surface with little shrinkage ('smooth surface') and few inflammatory aggregates with foreign large cells and few granulocytes and lymphocytes. **C**, **D** Conventional Atrium surface with shrinkage ('broken surface'), inflammatory infiltrate and calcification. HE. ×10.

In neither of the two groups were relevant intraoperative complications to be seen, and the duration of the procedure was similar in each.

After a postoperative period of 3 months – during which time all 22 experimental animals developed normally and showed a weight increase of approximately 3-fold (Atrium 274%, titanium-coated Atrium 321%) – the animals were killed. Laparoscopic inspection of the patch and its bed prior to autopsy revealed neither migration nor displacement of the implant in any of the animals. Nor did any animal show any signs of patch infection or a seroma. In 1 animal in the Atrium group, a tiny incisional hernia was observed at the site of the camera port – otherwise all trocar sites had healed well.

With regard to shrinkage, a significant difference favoring the titanium mesh was found (Atrium 14.9%; titanium-coated Atrium 8.8%; p = 0.031) (fig. 2). The histological investigation also revealed a smaller extent of inflammatory infiltrate for the titanium-coated mesh which, however, proved not to be significant (Atrium 17.3%; titanium-coated Atrium 12.4 %; p = 0. 15) (fig. 3). The Ki-67 expression – reflecting the foreign-body-in-



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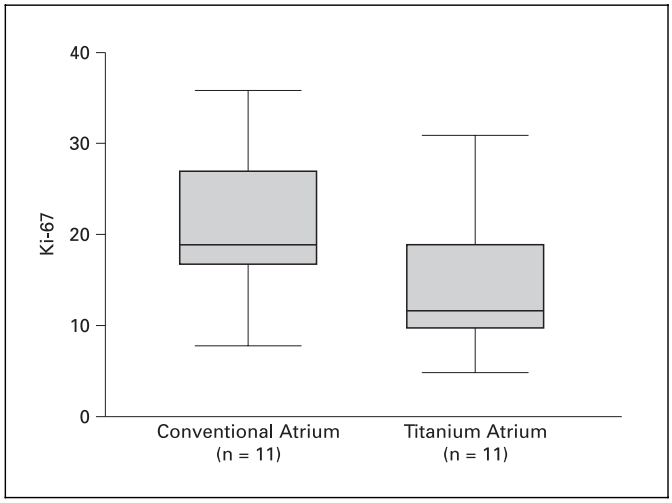

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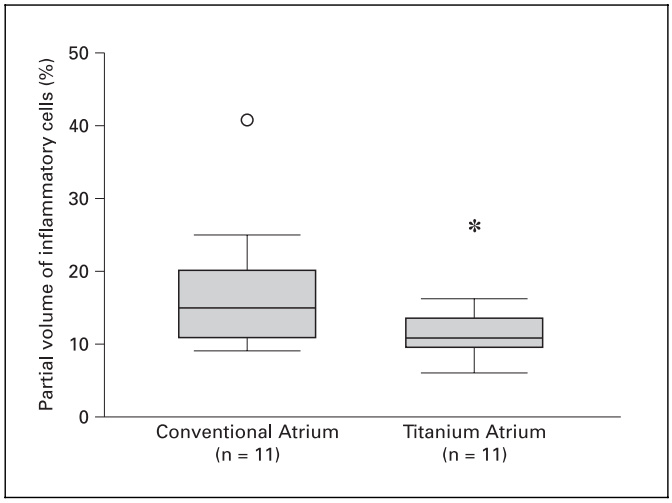

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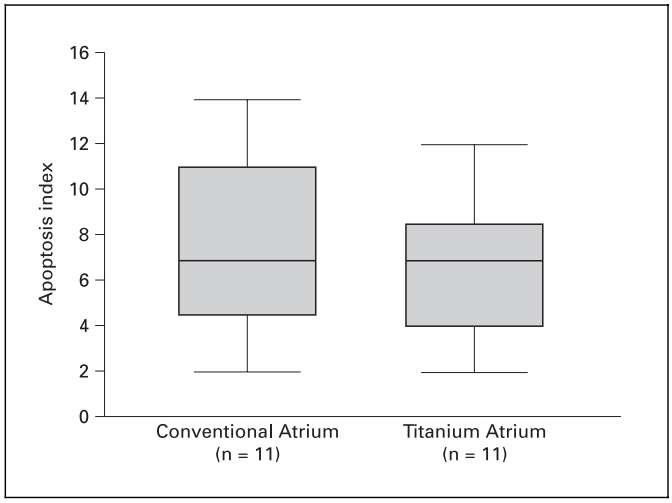

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Fig. 2. Shrinkage as a percentage of original mesh size (conventional Atrium mesh 14.9%, range 10–29%; titanium-coated Atrium 9.6%, range 3–17%); $p < 0.05$.

Fig. 3. Partial volumes of the inflammatory cells in % (conventional Atrium mesh 17.3%, range 9–41%; titanium-coated Atrium 31.4%, range 6–64%); NS.

Fig. 4. Ki-67 (conventional Atrium mesh 21.0, range 8–36; titanium-coated Atrium 15.0, range 5–31); NS.

Fig. 5. Apoptosis index (conventional Atrium mesh 7.6, range 2–14; titanium-coated Atrium 6.5, range 2–12%); NS.

duced proliferation rate – was also less pronounced in the titanium-coated group (Atrium 21; titanium-coated Atrium 15; $p = 0.093$) (fig. 4), but the difference was again not significant.

No inter-group difference was to be seen in the apoptosis rate, with the means, medians and ranges all being identical in both groups (Atrium 7.6; titanium-coated Atrium 6.5; $p = 0.49$) (fig. 5).

Discussion

Prompted by the fact that titanium is an excellent bioinert endoprosthetic material for use in trauma surgery, an attempt has now been made to utilize its favorable properties for prosthetic applications in hernia surgery. In view of the total lack of experience with any such material in hernial repair, the present study was conducted to investigate the potential utilizability of titanium in terms of healing behavior and chronic inflammatory reactions. With a titanium coating of only a few atoms in thickness

(approx. 30 nm), these meshes were, with the exception of a somewhat duller appearance of the surface, completely identical with the uncoated material, and showed no relevant differences with regard to rigidity, pore size and structure. Nor were any differences to be seen in terms of handling.

As has been shown in a number of earlier publications, foreign-body-induced inflammatory reactions show only minor changes after about 8 weeks in situ [9–14]. For this reason, the present study allowed for an implant in situ period of 3 months so as to ensure that the explantation would be carried out in a phase in which no major changes in the parameters investigated were to be expected.

Reports in the literature show that heavyweight polypropylene meshes undergo shrinkage – as a result of inflammatory reactions and scar formation – of up to 20–50% of their original size [10, 15]. In comparison, the shrinkage of the Atrium mesh in our experiment was, at 15%, somewhat more favorable. In the case of the titanium-coated mesh, however, the shrinkage characteristics were even more favorable (8.8%). This correlated with the partial volumes of the inflammatory cells (17.3 vs. 12.4), although a comparison of the mean values showed no statistical significance. There is a general consensus of opinion that the extent of the inflammatory reaction and resulting scar formation is determined both by the amount and the structure of the implant [10, 13, 15, 16]. Since the less pronounced inflammatory reaction and resulting more favorable shrinkage properties seen in this study were achieved with an identical amount of implanted material, it must be concluded that the effect is due entirely to the titanium coating/surface structure.

In a study by Duchrow et al. [17], the authors showed that human fibroblasts incubated at various cell concentrations with polypropylene meshes showed a significant increase in apoptosis with a largely unchanged proliferation rate. Unanswered is the question as to whether this influence on the apoptosis rate is due to a mechanical effect, or possibly to substances liberated by polymers, and their degradation products. It goes without saying that this in vitro study over a period of only 48 h cannot be compared without reservation with the present animal experiments during which the meshes remained in situ for 3 months. The fact that in our study a heavyweight polypropylene mesh is associated with the same apoptosis rates as an identical mesh with a metallic surface – and thus quite different surface properties – strongly suggests that the major influencing factor is of a mechanical nature.

Be that as it may, in the light of the collected data and the many years of utilization of polypropylene, it would appear unjustified to draw conclusions about cancerogenic potential based on apoptosis rates [18].

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References

1 Schumpelick V, Klinge U: Überlegungen zur Verfahrenswahl: Leistenhernienreparation mit oder ohne Mesh? Klinikarzt 2000;29:20–22.
2 Schumpelick V: Does every hernia demand a mesh repair? A critical review. Hernia 2001;5:5–8.
3 Herfarth C, Siewert JR: More attention to hernia surgery! Editorial. Chirurg 2000;71:41–42.
4 Klosterhalfen B, Klinge U, Hermanns B, Schumpelick V: Pathology of traditional surgical nets for hernia repair after long-term implantation in humans. Chirurg 2000;71:43–51.
5 Buck V, Ehrich H: Charakterrollen – Werkstoffeigenschaften durch Materialstruktur. Essener Unikate 2000;13:42–64.
6 Kuthe A, Saemann T, Tamme C, Köckerling F: Technique of total extraperitoneal endoscopic patch plasty. Zentralbl Chir 1998;123:1428–1435.
7 Tannapfel A, Geissler F, Köckerling F, Katalinic A, Hauss J, Wittekind C: Apoptosis and proliferation in relation to histopathological variables and prognosis in hepatocellular carcinoma. J Pathol 1999;187:439–445.
8 Tannapfel A, Nüsslein S, Fietkau R, Katalinic A, Köckerling F, Wittekind C: Apoptosis, proliferation, bax, bcl-2 and p53 status prior to and after preoperative radiochemotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 1998;41:585–591.
9 Bellon JM, Jurado F, Garcia-Moreno F, Corrales C, Carrera-San Martin A, Bujan J: Healing process induced by three composite prostheses in the repair of abdominal wall defects. J Biomed Mater Res 2002;63:182–190.
10 Klinge U, Klosterhalfen B, Müller M, Öttinger AP, Schumpelick V: Shrinking of polypropylene mesh in vivo: An experimental study in dogs. Eur J Surg 1998;164:965–969.
11 Hengirmen S, Aksoy F, Sencer H, Olcay E: Comparison of meshes for the repair of experimental abdominal wall defects. J Invest Surg 1998;11:15–25.
12 Rosengren A, Danielsen N, Bjursten LM: Inflammatory reaction dependence on implant localization in rat soft tissue models. Biomaterials 1997;18:979–987.
13 Schumpelick V, Klosterhalfen B, Müller M, Klinge U: Minimized polypropylene mesh for preperitoneal net plasty of incisional hernias. Chirurg 1999;70:422–430.
14 Marois Y, Cadi R, Gourdon J, Fatouraee N, King MW, Zhang Z, Guidoin R: Biostability, inflammatory response, and healing characteristics of a fluoropassivated polyester-knit mesh in the repair of experimental abdominal hernias. Artif Organs 2000;24:533–543.
15 Amid PK: Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997;1:15–21.
16 Goldstein HS: Selecting the right mesh. Hernia 1999;3:23–26.
17 Duchrow M, Windhövel U, Bethge T, Schwandner O, Markert U, Bruch HP, Broll R: Polypropylene synthetic mesh modifies growth of human cells in vitro. An experimental study. Chirurg 2002;73:154–160.
18 Ghadimi BM, Langer C, Becker H: The carcinogenic potential of biomaterials in hernia surgery. Chirurg 2002;73:833–838.