

Polyurethane foam-covered breast implants: a justified choice?

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Abstract. – OBJECTIVE: Even if the safety of the polyurethane prosthesis has been the subject of many studies and professional and public controversies. Nowadays, polyurethane covered implants are very popular in plastic surgery for the treatment of capsular contracture.

MATERIALS AND METHODS: We have identified 41 papers (1 is a communication of the FDA) by using search browsers such as Pubmed, Medline, and eMedicine. Eleven manuscripts have been used for an introduction, and the remaining thirty have been subdivided into three tables whose results have been summarized in three main chapters: (1) capsular formation and contracture, (2) complications, (3) biodegradation and cancer risk.

RESULTS: (1) The polyurethanic capsule is a well defined foreign body reaction characterized by synovial metaplasia, a thin layer of disarranged collagen fibers and a high vascularization. These features make possible a “young” capsule and a low occurrence of capsular contracture even over a long period (10 years); (2) the polyurethane implants may be difficult to remove but there is no evidence that they cause an increase in the other complications; (3) there is no evidence of polyurethane related cancer in long-term studies (after 5 years).

CONCLUSIONS: Polyurethane foam covered breast implants remain a valid choice for the treatment of capsular contracture even if it would be very useful to verify the ease of removal of the prosthesis and to continue investigations on biodegradation products.

Key Words:

Polyurethane, Breast implants, Mammary implants.

Introduction

Polyurethane has been used for medical devices since the second half of 20th century. It is formed by the reaction of polyols and toluendiisocyanate (TDI), and it's been useful in a variety

of ways in the health field, from cardiovascular devices (for example the inner surface of artificial hearts or micro-vascular prostheses) to breast implants.

Polyurethane foam-covered breast prostheses were projected by Ashley in 1970's¹⁻², and were a marked improvement over silicone breast implants which consisted of a smooth outer shell containing liquid silicone and were responsible for a high occurrence of capsular contracture.

Polyurethane implants were first characterized by a smooth foam-covered silicone shell and by the presence of three Y-shaped septa (Natural Y model). They also had a rough thick shell and were very easy to remove from the mammary pocket. This latter feature led to the creation of a new thin polyurethanic shell (1 mm thick) with laser seams, but easily detachable from the surface of the underlying silicone. Ashley applied it to four implant models: (1) Optimam: high profile, recommended for reconstructive surgery and with a unique internal septum, (2) Vogue: similar to the previous implant but with a low profile, (3) Mème: a low profile implant, used in aesthetic surgery, softer than the previous one because of the absence of septa, (4) Replicon: similar to Mème but with high profile.

The safety of the polyurethanic prosthesis has been the subject of many studies and professional and public controversies, culminating in April 1991 with the voluntary withdrawal by the manufacturer (Bristol-Myers Squibb, Skillman, NJ, USA) of the Mème implant from the US market because of the high risk of cancer in animals, due to significant quantities of 2,4 Toluene Diamine (2,4 TDA) derived from the degradation of the polyurethane shell, as the Food and Drug Administration (FDA) affirmed in the same year.³

In 1997, at the request of the FDA, Hester et al⁴ analyzed the urine and serum of 60 patients to determine whether women would be exposed to free 2,4 TDA as a consequence of the biodegradation of the polyurethane. As we shall

see later, the lack of evidence of carcinogenicity in humans, strengthening the earlier conclusions of the Health Protection Branch (Fredericton, NB E3B 5G4, Canada)⁵, led the FDA to declare that the cancer risk was negligible and that there was no need to remove the polyurethane breast implant⁶.

At the moment this kind of implant is produced by two manufacturers (Polytech and Silimed) and legally sold in Europe and South America. The implants are used in plastic surgery for the treatment of capsular contracture and are made up of a textured silicone breast implant, anatomic or round shaped, covered by a 1000µm layer of polyurethane foam bonded more thickly to the surface of the silicone shell⁷.

In this review we analyzed the literature on polyurethane breast implants with the aim of evaluating whether they represent a valid choice.

Materials and Methods

Search browsers such as Pubmed, Medline, and eMedicine were used to identify the following search words, either alone or in combination: “breast capsule”, “polyurethane breast prosthesis”, “foam covered breast implants”, and “toluendiamine”. We have identified 41 papers (1 is a communication of the FDA), 11 of which have been used for an introduction, and the remaining 30 papers have been subdivided into three tables summarizing the results in three main chapters: (1) capsular formation and contracture, (2) complications, (3) biodegradation and cancer risk.

Capsule Formation and Contracture (Table I)

The capsule is a dynamic inflammatory process represented by a foreign body reaction

Table I. Capsule formation and contracture.

Year	Authors	Model	Type of study	Conclusions
1978	Smahel ¹⁵	Human	Case series	Well defined foreign body reaction and vacuolated spaces with polyurethane fragments
1984	Brand ²⁷	Animal (mice)	Experimental	Macrophages and giants cells; microcapsules with fragments later replaced with fibroblasts and collagen; prevent capsular contracture
1985	Pennisi ¹⁶	Human	Case series	150 patients: breast firmness in 4 cases plus capsular contracture; breast softness in the others
1989	Baudelot ¹⁷	Human	Case series	Low occurrence of capsular contracture in polyurethane implants
1990	Caffee ²⁹	Animal (rabbits)	Experimental	Asymptomatic capsular contracture
1992	Barone ³⁰	Animal (rabbits)	Experimental	Low capsular contracture
1993	Sinclair ¹⁸	Human	Case series	Capsular contracture in 48% (36/75)
1994	Bucky ³¹	Animal (rabbits)	Experimental	Soft capsule; later deposition of fibrotic tissue
1995	Raso ¹⁹	Human	Case report	Presence of synovial metaplasia
1997	Wang ²⁰	Human	Case report	Foreign body reaction; lasting vascularization; soft capsule; low incidence of capsular contracture
2006	Handel ²¹	Human	Population based	Low occurrence of capsular contracture in PU implants for almost 10 years
2006	Prado ²²	Human	Letter to editor (case series)	Mirror-like aspect of the polyurethane capsule
2007	Vasquez ²³	Human	Retrospective study	Soft breast after 6 weeks postoperative; polyurethane fragments in capsule; low capsular contracture due to disoriented collagen fibers
2008	Mendes ³²	Animal (rats)	Experimental	Thick capsule; chronic granulomatosis
2010	Bassetto ²⁴	Human	Case series	Synovial metaplasia, foreign body reaction after 5 years; parallel collagen fibers
2010	Viera ³³	Animal (feminine rats)	Experimental	Thick capsule; thin collagenous layer; enlargement of non collagenous layer; high neovascularization and VEGF; high polymorphonucleates, TGF-β, α smooth muscle actin. Low capsular contracture; soft breast
2011	Dini ²⁵	Human	Letter to editor (case series)	Great adhesion between capsule and implant surface; low incidence of capsular contracture for 10 yrs
2011	de la Peña Salcedo ³⁹	Human	Retrospective	Capsular contracture in 0.4%
2012	Mossaad ²⁶	Human	Case report	Synovial metaplasia and giant cells

due to the presence of the breast implant. For textured implants, it is clear that this process will establish itself during the first 3-4 weeks⁸⁻¹² and that it is characterized by different cell types depending on the stage of capsular formation. The first stage is characterized by macrophages attempting to isolate the foreign body; the T and B lymphocytes have the task of causing the antibody response and promoting the proliferation of fibroblasts with consequent deposition of extracellular matrix¹³⁻¹⁴.

It is possible to divide the textured capsule into three histological layers: (1) the intimal zone that is directly in contact with the surface of the prosthesis and it is featured by the presence of macrophages, fibroblasts, and, in some cases, a pseudo-epithelium called synovial metaplasia; (2) the intermediate layer characterized by the presence of parallel or disoriented collagen fibers (their orientation depends on the surface of the prosthesis and the age of the implant); (3) the transition layer, the outer part of the capsule, which is connected to the surrounding tissue (the pectoralis muscle or the mammary gland).

Nowadays it is well established that the persistent presence of the implant is likely to cause, in some patients, the transformation of a physiological foreign body reaction into a chronic one, named capsular contracture, characterized by a progressive circumferential contraction around the prosthesis. This contraction is due to the parallel alignment of the collagen fibers and can result in a hardened breast, breast pain and the necessity of performing a second operation (capsulectomies or capsular removal) with the replacement of the prosthesis.

The etiology of capsular contracture is still under discussion, but it seems clear that a "young capsule" (the presence of synovial metaplasia and/or inflammatory reaction, an increased vascularity, and the disarray of the collagen fibers), may be a protective factor.

In order to understand what the features of the polyurethane capsule were, but especially whether any differences from the silicone capsule may promote or prevent capsular contracture, many studies have been carried out since 1970 on both the human model¹⁵⁻²⁶ and the animal model²⁷⁻³³.

Despite the different origins of the samples, they have indicated in both the human and animal models a great softness of the breast and a low occurrence of contracture, even in the long term (10 years)^{21,25}. Compared with the capsule

from the smooth and textured implants, the polyurethane one consists of: (1) inflammatory cells and blood vessels that surround the polyurethane particles and (2) a loosely organized and less fibrous collagen layer. More in particular the capsule has been described as: (1) a high, well-represented and defined foreign body response that individually surrounds the polyurethane fragments ("microencapsulation"); (2) the presence of synovial metaplasia; (3) an increased durable vascularization that is demonstrated immunohistochemically by a high presence of Vascular Endothelial Growth Factor (VEGF); (4) the presence, in most cases, of a thin layer of disoriented, sometimes crossed, collagen fibers characterized by a reduction in the proportion of type III collagen; (5) the mirror-like appearance of the capsule due to the strong adhesion of the capsule to the implant surface. This feature can be explained as the sponge-like polyurethane coating of the implant "printed" on the inner layer of the capsule.

Other Complications (Table II)

The implant of a mammary prosthesis can lead to the onset not only of capsular contracture, but also of other early or late complications such as hematoma, seroma, breast pain, infection and skin rash.

In order to verify the prevalence and the type of complications related to the polyurethane prostheses, and especially whether there was a difference from silicone implants, we analyzed studies performed on human models over the last 30 years (letters to editors, case reports and retrospective studies)^{17,20-23, 25-27}.

Even if the studies have reported some cases of delayed pain and/or hematoma, they showed, more generally, a lower appearance of infections and seroma, a lesser "heavy breast" sensation and a lower risk of implant rupture. It is interesting to note that some authors, such as Prado et al²² and more recently Mirò¹², Dini and Mossaad²⁵⁻²⁶, have talked about the loss of the surgical plane of dissection. This characteristic makes it necessary to perform a very difficult removal of the prosthesis, with a high risk of bleeding and sometimes having to cut part of the pectoralis muscle in association to the "capsular-prosthetic complex". This difficulty has been described in both primary and secondary surgery, so it seems to be independent of the presence of other complications, as for example contracture or hematoma.

Table II. Other complications.

Year	Authors	Model	Type of study	Conclusions
1986	Jabaley ³⁴	Human	Case report	Late breast pain disappeared after explantation
1989	Baudelot ¹⁷	Human	Case series	No increased complications; difficulty of insertion
1997	Wang ²⁰	Human	Case report	2 cases of late hematoma; infection, skin itchy rash; wrinkling and late pain
2006	Handel ²¹	Human	Population based	Low occurrence of infection; relative high risk of haematoma (13/568), low feeling of breast heaviness; low risk of implant rupture; earlier reoperation time
2006	Prado ²²	Human	Letter to editor (case series)	3 ruptures and 1 retro muscular pain; great intraoperative bleeding; difficult removal due to the lack of a surgical plane dissection; great adhesion of the capsule to the implant surface
2007	Vazquez ²³	Human	Case series	Low occurrence of late sieroma
2011	Dini ²⁵	Human	Letter to editor (case series)	Absent surgical plane of dissection; thick capsule; great adhesion to the muscle

Biodegradation and Cancer (Table III)

Since their creation polyurethane implants have been analyzed for their tendency to trigger breast cancer. Scholars suspected a correlation between breast cancer and the products of polyurethane degradation. In 1991, the FDA published a report explaining that the 2,4 TDA produced during biodegradation could promote cancer and that it was appropriate to suspend the sale of the PU implants and to continue with the experimental studies³.

For this reason, the 1990's were characterized by contrasting opinions^{3-5,7,35-38}: if on the one hand some studies supported carcinogenicity,

others underlined the lack of data to substantiate the toxicity of polyurethane. These last studies showed how the amount of 2,4 TDA produced was not carcinogenic for humans.

To confirm this thesis, Hester et al^{4,7} published studies in 1997 and in 2001 in which they analyzed the urine and serum of 60 patients with the aim of finding free 2,4 TDA. In this study the authors stabilized the samples at a physiologic pH and temperature, in order to avoid the separation of the TDA from the oligomers resulting from the biodegradation of the polyurethane. Using a standard methodology for risk assessment formalized by the National Academy of Science and

Table III. Biodegradation and cancer.

Year	Authors	Model	Type of study	Conclusions
1988	Brand ²⁸	Animal (mice)	Experimental <i>in vivo</i>	Less tumorigenic than uncoated implants
1991	Szycher ³⁵	<i>In vitro</i>	<i>In vitro</i>	Risk of cancer of 1:400.000.000 in standard risk analysis for Physiological conditions
1991	Boyes ⁵	Review	Expert opinion	Further studies required
1993	Hagmar ³⁷	Human	Cohort study	No association between isocyanate exposure and cancer
1993	Hagmar ³⁸	Human	Cohort study	No association between toluendiisocyanate and cancer
1997	Hester ⁴	Human	Case series/ Expert opinion	Risk of cancer of 1:1.000.000 in long term; the biodegradation occurs for 2 years after surgery
1998	Luu ³⁶	<i>In vitro</i> and animal	<i>In vitro</i> and animal	High accumulation of products from biodegradation in the serum protein; risk for breast and liver cancer of 1:400.000 in the lifetime
2001	Hester ⁷	Review	Expert opinion	No carcinogenicity
2002	Sorahan ⁴²	Human	Retrospective	No association with cancer
2011	de la Peña-Salcedo ³⁹	Human	Retrospective	The polyurethane implants are safe
2012	Pan ⁴⁰	Human	Cohort/ retrospective	No augmented risk in long term; the authors showed a 7-fold increased risk of cancer in the first 5 years after surgery

previously used by the FDA, the authors calculated the lifetime cancer risk as 1 in 1,000,000 patients. The study, carried out at the request of the FDA and approved in its methods by the FDA itself, led the Food and Drug Administration to declare that the cancer risk was negligible and to confirm the hypothesis made in 1995: “it is unlikely that even one of the estimated 110,000 women with polyurethane-covered implants will get cancer as a result of exposure to TDA”⁶. This risk appraisal has also agreed with the findings of the Canadian Health Protection Branch in 1991: “the risk of breast cancer is very small” and “surgical removal of polyurethane foam covered breast implants solely for reasons of potential risk of cancer does not appear to be indicated”⁵.

These data were recently confirmed by a retrospective study on 996 implants³⁹: the results showed that, during a 15-year follow-up, the polyurethane foam-covered breast implants were proven safe and there was no evidence of cancer.

As we shall explain later in the discussion paragraph, a noteworthy but arguable work was published by Pan et al⁴⁰. Using the same cohort population of 2006, this report presents an extension of the results of an earlier perspective study⁴¹ in which the authors analyzed the potential risk of cancer in a cohort of Ontario and Quebec women having bilateral breast augmentation. In particular they studied 24558 patients who underwent bilateral breast augmentation between 1974 and 1989; 2569 patients out of 24558 (10.5%) received polyurethane breast prostheses, and in 2006 only 15 cases, with a polyurethanic subglandular implant, were affected by breast cancer.

With the aim of calculating the incident rate risk, the authors used statistical software and models such as the multivariable Poisson regression and the Epicure software, and reported a sevenfold increased potential rate of cancer appearance during the first years after the subglandular implant of the polyurethanic prostheses. This risk has progressively decreased, approximately to 0%, over the years.

Discussion

Capsule Formation and Contracture

The foreign body reaction to the polyurethane implant is characterized by the presence of a high number of VEGF and by “microencapsulation” around the polyurethane fragments derived from

the biodegradation of the prosthesis shell. These features might explain the softness of the breast if we consider the improved and lasting vascularization, the continuous stimulation, due to the polyurethane biodegradation and subsequently to that of the silicone, and the mirror-like aspect of the capsule due to the strong adhesion-integration between polyurethane and the surrounding tissue, can preserve a “young” capsule. The young capsule and the presence of microcapsules around the fragments can avoid, for almost 10 years^{21,25}, circumferential formation and contraction of the capsular tissue.

This time frame for capsular contracture is very different in the silicone capsule. These one, in fact, is definitely established in 3-4 weeks and it's featured by a less vascularization and inflammation than PU and, most of all, the capsule presents an aligned fibrotic layer with a higher number of type III collagen fibers. These characteristics permit a circumferential contraction of the capsular tissue with the consequent capsular contracture even after the first postoperative months.

Other Complications

Despite the fact that there are few studies showing no evidence of an increased prevalence in complications, the important point is that these prostheses can cause the lack of a surgical plane of dissection. The strong adhesion of the capsule to the surrounding tissue (the mirror-like aspect) causes a kind of integration between the implant and the muscles or the mammary gland. This integration has been described as a difficulty to discern the presence of the implant during an external palpation and, intraoperatively, as the absence of a clearly defined plane of dissection. The absence and the well represented muscular and capsular vascularization may cause, as reported, a significant and not clearly identifiable bleeding which leads the surgeon to remove part of the pectoralis muscle. This complication can cause not only aesthetic damage, but also a loss of muscle function. This could preclude their use especially in cosmetic surgery: even if the mirror-like appearance of the capsule and its strong adhesion to the implant can reduce the occurrence of capsular contracture, in the subglandular implant, for example, these features may force the surgeon to remove part of the mammary gland too, mimicking the outcome of a quadrantectomy or, in extreme cases, a mastectomy.

Biodegradation and Cancer

Although the chemistry and the pharmacokinetic of the polyurethane polymer have already been clarified, the controversies over the cancer risk are still going on. The doubts may arise from the idea that the rat-model, used to test carcinogenicity, cannot be related to the human body because of the difference in both the pharmacokinetic and the carcinogenicity itself (we must not forget that workers exposed to high levels of 2,4-TDA have shown no increased risk of cancer of any type)^{37-38,42}.

As for the potential carcinogenicity during the first years reported by Pan et al⁴⁰, we think that instances of bias need be considered. First of all, the authors themselves noted that the possibility that polyurethane directly contributes to a real increased risk is tenuous, especially if we consider that the “estimates were based only on a small number of incident cases which increases the possibility that the results could be due to chance”.

In addition, we must take into consideration the collection period of the patients. The authors have considered the patients who underwent breast augmentation between 1974 and 1989, but this is the period of the very first kind of polyurethane implants. At the beginning these implants were characterized by an easily removable polyurethanic shell that could get detached from the silicone shell; we believe that this easy detachment could be responsible for both the large amount of 2,4 TDA and, consequently, for the increased cancer risk. The organism had to metabolize not only the small fragments but maybe entire parts of the polyurethane shell that could quickly get detached. Nowadays, the implants have a polyurethanic shell that is more firmly bonded and not easily detachable from the underlying silicone, so that the body has to deal “only” with the small fragments derived from the slow biodegradation of the polyurethane.

Basing ourselves on these last considerations, we think that further investigation is required to verify the possibility of increased risk of cancer in the short term; however, in order to avoid a “fake positivity”, it is also mandatory to use the current kind of polyurethane foam covered breast implants.

Conclusions

Considering that the polyurethane foam-covered breast implants induce the formation of a well vascularized “young” capsule, this kind of implant remains a valid choice for the treatment

of capsular contracture. However, in order to verify the possible risk of cancer in the short term and to avoid aesthetic and functional damage due to the difficult removal of the polyurethane implants, it is necessary to carry out further investigation on these useful breast prostheses.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

- 1) ASHLEY FL. A new type of breast prosthesis. Preliminary report. *Plast Reconstr Surg* 1970; 45: 421-424.
- 2) ASHLEY FL. Further studies on the Natural-Y breast prosthesis. *Plast Reconstr Surg* 1972; 49: 414-419.
- 3) SPURGEON D. The Mème implant creates a scientific storm. *CMAJ* 1991; 145: 54-60.
- 4) HESTER TR JR, FORD NF, GALE PJ, HAMMETT JL, RAYMOND R, TURNBULL D, FRANKOS VH, COHEN MB. Measurement of 2,4-toluenediamine in urine and serum samples from women with Mème or Replicon breast implants. *Plast Reconstr Surg* 1997; 100: 1291-1298.
- 5) BOYES DC, ADEY CK, BAILAR J, BAINES C, KERRIGAN C, LANGLOIS P. Safety of polyurethane-covered breast implants. Expert Panel on the Safety of Polyurethane-covered Breast Implants. *CMAJ* 1991; 145: 1125-1132.
- 6) FOOD AND DRUG ADMINISTRATION UPDATE: Study of TDA released from polyurethane foam-covered breast implants. (June 27, 1995).
- 7) HESTER TR JR, TEBBETTS JB, MAXWELL GP. The polyurethane-covered mammary prosthesis: facts and fiction (II): a look back and a “peek” ahead. *Clin Plast Surg* 2001; 28: 579-586.
- 8) SMAHEL J. Structure of the capsule around silicone elastomer implants. *Chir Plastica* 1980; 5: 119-125.
- 9) BROHIM RM, FORESMAN PA, HILDEBRANDT PK, RODEHEAVER GT. Early tissue reaction to textured breast implant surfaces. *Ann Plast Surg* 1992; 28: 354-362.
- 10) SMAHEL J, HURWITZ PJ, HURWITZ N. Soft tissue response to textured silicone implants in an animal experiment. *Plast Reconstr Surg* 1993; 92: 474-479.
- 11) ESCUDERO FJ, GUARCH R, LOZANO JA. Reacción tisular a las prótesis mamaria. Contractura capsular periprotésica. (Tissue reaction to breast prostheses. Periprosthetic capsular contracture). *An Sist Sanit Navar* 2005; 28: 41-53.
- 12) MIRÓ AL. Próteses mamárias revestidas com poliuretano: avaliação de 14 anos de experiência (Polyurethane-coated silicone breast implant: evaluation of 14 years’ experience). *Rev Bras Cir Plast* 2009; 24: 296-303.

- 13) BASSETTO F, SCARPA C, VINDIGNI V, DORIA A. The periprosthetic capsule and connective tissue diseases: a piece in the puzzle of autoimmune/autoinflammatory syndrome induced by adjuvants. *Exp Biol Med* (Maywood) 2012; 237: 1117-1122.
- 14) SCARPA C. The immunological response to breast implant: the role of cells and cytokines in the periprosthetic capsule and their involvement in the onset of the autoimmune diseases. Thesis of PhD in Padua research.
- 15) SMAHEL J. Tissue reactions to breast implants coated with polyurethane. *Plast Reconstr Surg* 1978; 61: 80-85.
- 16) PENNISI VR. Polyurethane-covered silicone gel mammary prosthesis for successful breast reconstruction. *Aesthetic Plast Surg* 1985; 9: 73-77.
- 17) BAUDELLOT S. Evaluation after 4 years' experience with breast implants coated with microthane" *Ann Chir Plast Esthet* 1989; 34: 279-284.
- 18) SINCLAIR TM. Biodegradation of the polyurethane foam covering of breast implants. *Plast Reconstr Surg* 1993; 92:1003-1013; discussion 1014.
- 19) RASO DS, GREENE WB. Synovial metaplasia of a periprosthetic capsule surrounding a polyurethane foam breast prosthesis. *Ann Plast Surg* 1995; 35: 201-203.
- 20) WANG BH, CHANG BW, SARGEANT R, MANSON PN. Late capsular hematoma after breast reconstruction with polyurethane-covered implants. *Plast Reconstr Surg* 1998; 102: 450-452.
- 21) HANDEL N, CORDRAY T, GUTIERREZ J, JENSEN JA. A long-term study of outcomes, complications, and patients satisfaction with breast implants. *Plast Reconstr Surg* 2006; 117, 757-767.
- 22) PRADO AS, ANDRADES P, BENITEZ S. A word of caution on the explanation of polyurethane breast implants. *Plast Reconstr Surg* 2006; 117: 1655-1657.
- 23) VAZQUEZ G, PELLON A. Polyurethane-coated silicone gel breast implants used for 18 years. *Aesth Plast Surg* 2007; 31: 330-336.
- 24) BASSETTO F, SCARPA C, CACCIALANZA E, MONTESCO MC, MAGNANI P. Histological features of periprosthetic mammary capsule: silicone vs polyurethane. *Aesth Plast Surg* 2010; 34: 481-485.
- 25) DINI M, GIORDANO V, QUATTRINI LI A, MORI A, NAPOLI S. Double capsules: our experience with polyurethane-coated silicone breast implants. *Plast Reconstr Surg* 2011; 128: 819-821.
- 26) MOSSAAD BM, FRAME JD. Correction of breast contour deformities using polyurethane breast implant capsule in revisional breast surgery. *J Plast Reconstr Aesthet Surg* 2012; 65:1425-1429
- 27) BRAND KG. Foam-covered mammary implants. *Clin Plast Surg* 1984; 73: 498.
- 28) BRAND KG. Foam-covered mammary implants. *Clin Plast Surg* 1988; 15: 533-539.
- 29) CAFFEE HH. Polyurethane foam-covered implants and capsular contracture: a laboratory investigation. *Plast Reconstr Surg* 1990; 86: 708-714.
- 30) BARONE FE, PERRY L, KELLER T, MAXWELL GP. The biomechanical and histopathologic effects of surface texturing with silicone and polyurethane in tissue implantation and expansion. *Plast Reconstr Surg* 1992; 90: 77-86.
- 31) BUCKY LP, EHRLICH HP, SOHONI S, MAY JW JR. The capsule quality of saline-filled smooth silicone, textured silicone, and polyurethane implants in rabbits: a long-term study. *Plast Reconstr Surg* 1994; 93: 1123-1133.
- 32) MENDES PR, BINS-ELY J, LIMA EA, VASCONCELLOS ZA, D'ACAMPORA AJ, NEVES RD. Histological study on acute inflammatory reaction to polyurethane-coated silicone implants in rats. *Acta Cir Bras* 2008; 23: 93-101.
- 33) VIEIRA VJ, D'ACAMPORA AJ, MARCOS AB, DI GIUNTA G, DE VASCONCELLOS ZA, BINS-ELY J, D'EÇA NEVES R, FIGUEIREDO CP. Vascular Endothelial Growth Factor overexpression positively modulates the characteristics of periprosthetic tissue of polyurethane-coated silicone breast implant in rats. *Plast Reconstr Surg* 2010; 126: 1899-1910.
- 34) JABALEY ME, DAS SK. Late breast pain following reconstruction with polyurethane-covered implants. *Plast Reconstr Surg* 1986; 78: 390-395.
- 35) SZYCHER M, SICILIANO AA. An assessment of 2,4 TDA formation from Surgitek polyurethane foam under simulated physiological conditions.. *J Biomater Appl* 1991; 5: 323-336.
- 36) LUU HM, HUTTER JC, BUSHAR HF. A physiologically based pharmacokinetic model for 2,4-toluenediamine leached from polyurethane foam-covered breast implants. *Environ Health Perspect* 1998; 106: 393-400.
- 37) HAGMAR L, STRÖMBERG U, WELINDER H, MIKOCZY Z. Incidence of cancer and exposure to toluene diisocyanate and methylene diphenyldiisocyanate: a cohort based case-referent study in the polyurethane foam manufacturing industry. *Br J Ind Med* 1993; 50: 1003-1007.
- 38) HAGMAR L, WELINDER H, MIKOCZY Z. Cancer incidence and mortality in the Swedish polyurethane foam manufacturing industry. *Br J Ind Med* 1993; 50: 537-543.
- 39) DE LA PEÑA-SALCEDO JA, SOTO-MIRANDA MA, LOPEZ-SALGUERO JF. Back to the future: a 15-year experience with polyurethane foam-covered breast implants using the partial-subfascial technique. *Aesthetic Plast Surg* 2012; 36: 331-338.
- 40) PAN SY, LAVIGNE E, HOLOWATY EJ, VILLENEUVE PJ, XIE L, MORRISON H, BRISSON J. Canadian breast implant cohort: extended follow-up of cancer incidence. *Int J Cancer* 2012; 131: E1148-1157.
- 41) BRISSON J, HOLOWATY EJ, VILLENEUVE PJ, XIE L, UGNAT AM, LATULIPPE L, MAO Y. Cancer incidence in a cohort of Ontario and Quebec women having bilateral breast augmentation. *Int. J. Cancer* 2006; 118: 2854-2862.
- 42) SORAHAN T, NICHOLS L. Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958-98. *Occup Environ Med* 2002; 59: 751-758.