

FRANCISCO CLARO DE OLIVEIRA JUNIOR

**INDICAÇÕES E SEGURANÇA DA
LIPOENXERTIA AUTÓLOGA NA MAMA**

Dissertação de Mestrado

ORIENTADOR: Prof. Dr. AARÃO MENDES PINTO NETO

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INDICAÇÕES E SEGURANÇA DA LIPOENXERTIA AUTÓLOGA NA MAMA

FRANCISCO CLARO DE OLIVEIRA JUNIOR

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Dedico este trabalho...

**Ao meu avô, Aparecido Parpinelli (*in memoriam*),
pela formação moral e exemplo de vida.**

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pelo suporte, ajuda e estímulo no desenvolvimento de meus estudos.**

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Símbolos, Siglas e Abreviaturas

ACR – *American College of Radiology*

ADCTs – Adipócitos Derivados de Células-Tronco

ASPRS – *American Society of Plastic and Reconstructive Surgeons*

BI-RADS – *Breast Imaging-Reporting and Data System*

MMG – Mamografia/ *Mammography*

NR – *Not Referred*

NS – *Not Specified*

NU – Não Utilizado

PRISMA – *Preferred Reporting Items for Systematic Review and Meta-Analyses*

RNM – Ressonância Nuclear Magnética

TRAM – *Transverse Rectus Abdominus Musculus*

US – Ultrassonografia

Resumo

Introdução: a enxertia de gordura autóloga lipoaspirada na topografia mamária permanece controversa quanto a efetividade para fins estéticos e reparadores e a segurança do procedimento. O objetivo do estudo foi realizar uma revisão sistemática da literatura sobre a aplicabilidade clínica do procedimento e a segurança em relação às complicações clínicas, as alterações radiológicas e o risco oncológico. **Métodos:** busca digital na Cochrane Library, MEDLINE, EMBASE e SCIELO, entre julho de 1986 a junho de 2011. A revisão incluiu artigos com casos originais, em mulheres, enxertia de gordura autóloga recém-lipoaspirada, topografia mamária, descrição de complicações clínicas e/ou alterações radiológicas e/ou recidiva de câncer mamário. **Resultados:** Foram incluídos nesta revisão 60 artigos, que totalizaram 4739 casos. A lipoenxertia mamária foi utilizada satisfatoriamente para o tratamento estético e reconstrutivo das mamas. Foram identificadas 155 complicações clínicas, sendo 60% de endurecimento e/ou nodulação palpável. A sua incidência, avaliada em 21 estudos, foi de 64/3015. A incidência de alterações radiológicas, avaliada em 17 estudos, foi de 266/2560. Imagens compatíveis com cisto à mamografia e/ou ultrassonografia e/ou ressonância

nuclear magnética foram identificadas em mais da metade destes casos. Não foi identificado um único caso de câncer de mama primário. A incidência de recorrência local foi avaliada em três estudos, sendo 14/616 e não foi diferente nas mulheres mastectomizadas sem lipoenxertia. **Conclusão** : Foi identificada ampla aplicabilidade clínica da lipoenxertia autóloga na mama com baixo índice de complicações e sem evidência de comprometimento na detecção do câncer de mama. Em relação ao risco oncológico, pelo pequeno número de casos, os resultados embora aparentemente seguros, não foram conclusivos.

Palavras-Chave: mama, enxerto de gordura, lipoenxertia, transplante de gordura, gordura autóloga.

Summary

Background: Autologous fat grafting to the breast for cosmetic and reconstructive purposes is still controversial regarding the safety and efficacy of the procedure. The aim of this study was to conduct a systematic review on clinical applicability and safety of the technique concerning clinical complications, radiographic changes and oncological risk. **Methods:** an online search of the Cochrane Library, MEDLINE, EMBASE and SCIELO was conducted from July 1986 to June 2011. Studies included original articles of autologous liposuctioned fat grafting to the female breast with description of clinical complications and/or radiographic changes and/or local breast cancer recurrence. **Results:** This review included 60 articles (total: 4739 patients). Thirty studies use fat grafting for augmentation and 41 for reconstructive procedures. It was satisfactory in aesthetic and reconstructive breast treatment. Clinical complications incidence identified in 21 studies was 64/3015, the majority of them were induration and/or palpable nodulation. The incidence of radiographic changes was 266/2560 in 17 studies. Fifty per cent of Images changes were consistent with cysts on mammography and/or ultrasound and/or magnetic resonance. There were no cases of primary breast cancer. The incidence of local recurrence (14/616) was evaluated in just

three studies, and among them only one is prospective and none is randomised.

Conclusion a broad clinical applicability of autologous fat grafting to the breast was found. Complication rate was low and there was no evidence of interference with breast cancer detection. Although apparently safe, study results concerning oncological risk are not clear at present.

Key words: Breast, fat grafting, lipofilling, fat transplantation, autologous fat.

1. Introdução

O tecido adiposo, presente no corpo humano no meio subcutâneo e intra-abdominal, tem como função primordial o armazenamento de energia. Entretanto, é um órgão com importantes funções metabólicas e hormonais. No meio subcutâneo, sua principal função é de isolamento térmico. No meio intra-abdominal, tem a função primordial de reserva energética e proteção de órgãos vitais. Neste meio, embora exista grande quantidade de adipócitos em regiões perigonadal e perivisceral, a principal reserva de células de gordura está localizada no grande omento ou epíplon.

No âmbito cirúrgico, o tecido adiposo vem sendo intensamente utilizado por várias especialidades como matéria-prima para o reparo e a reconstrução de importantes estruturas corporais há mais de 100 anos. Em 1889, Van Der Meulen *apud* Mojallal e Foyatier (1), relatou a interposição do epíplon para o tratamento de hérnia diafragmática. Neuber (1893) *apud* Mojallal e Foyatier (1), enxertou um fragmento de gordura subcutânea do braço para a correção de uma cicatriz facial secundária a uma osteíte tuberosa.

O uso de adipócitos na cirurgia reparadora é descrito como fonte da primeira reconstrução mamária relatada, quando Czerny (1895) *apud* Beekman, Hage, Jorna e Mulder (2), utilizou um grande lipoma do dorso para reconstrução de uma seqüela mamária deixada pela exérese de uma lesão benigna da mama. Em 1910, Lexer *apud* Mojallal e Foyatier (1), foi o primeiro a relatar a utilização de gordura em bloco do tecido subcutâneo na forma de enxerto nas regiões malar e labial como tratamento estético contra o envelhecimento. Também Brunning (1911) *apud* Mojallal e Foyatier (1), relatou o uso de pequenos fragmentos de gordura sob a pele do nariz para melhorar os contornos nasais.

Em 1925, Lexer *apud* Mojallal e Foyatier (1), publicou estudos sobre a sobrevivência do tecido adiposo subcutâneo, transplantado em bloco não pediculado, e relatou um caso de lipoenxertia na face para o tratamento da síndrome de Romberg, também conhecida como hemiatrofia facial progressiva, caracterizada pela atrofia de um dos lados da face. A partir de então, a utilização de tecido adiposo em bloco não pediculado do subcutâneo ganhou grande popularidade em várias especialidades médicas. Na região mamária, a evolução da implantação de tecido adiposo prosseguiu com Lexer (1931) *apud* Mojallal e Foyatier, que relatou um caso de reconstrução mamária após mastectomia, por mastopatia cística crônica, com gordura da região subcutânea da axila; entretanto o resultado não foi satisfatório.

Com os resultados precários da lipoenxertia em bloco na região mamária e na busca de melhorar a sobrevivência dos adipócitos transplantados, em 1941, May *apud* Billings e May (3) apresentou um caso de reconstrução

mamária bilateral. Em uma mama foi utilizada gordura isoladamente e na outra a gordura foi enxertada juntamente com a fáscia; nesta última, com o propósito de preservar melhor a gordura.

Novas tentativas com a utilização de adipócitos na topografia mamária são apresentadas a partir de relatos de aumento da mama com enxerto dermogorduroso (4). Em 1957, Scrocher *apud* Mojallal e Foyatier (1), relatou o uso de enxerto de gordura subcutânea em bloco. Neste mesmo ano, Peer (5) descreveu o tratamento de um caso de Síndrome de Poland com o uso de enxerto dermogorduroso retirado da região abdominal. Ainda na década de 50, as limitações do enxerto de gordura subcutânea em bloco na topografia mamária passaram a ganhar importância e novos estudos surgiram nesta área (5-6).

A partir de então, novas técnicas de reconstrução mamária com adipócitos foram divulgadas. Em 1963, o cirurgião romeno Kiricuta (7) relatou 10 casos bem sucedidos com a utilização do retalho pediculado de omento para a reconstrução de mama. Arnold, Hartrampf e Jurkiewicz (8) descreveram uma técnica de reconstrução mamária com implante mamário recoberto por omento pediculado e enxerto de pele parcial, e em 1979 foi descrita a utilização do epíplon isoladamente nas técnicas de reconstrução de mama com preservação cutânea (9).

No início da década de 1980, Illouz (10-11) criou a lipoaspiração e juntamente com a técnica apresentou o enxerto de gordura. Em 1985, Illouz e Fournier (12) também propuseram a utilização imediata da gordura aspirada,

sem qualquer preparo, para a enxertia, criando desta forma um novo conceito na utilização do tecido adiposo como tecido de preenchimento e reconstrução. A partir de então, observou-se que a gordura lipoaspirada e conseqüentemente microfragmentada, quando enxertada, apresentava maior sobrevida que a gordura em bloco para aplicação em diversas regiões corporais.

Em 1987, Bircoll (13) e Bircoll e Novack (14) apresentaram casos com excelentes resultados através de lipoenxertia em microtúneis para aumento e reconstrução mamária. Entretanto, estes resultados não foram facilmente reproduzíveis quando realizados sem o conceito de microlipoenxertia, dando início a uma nova era de intensificação de estudos e discussões sobre o uso de tecido adiposo em topografia de mama feminina.

A partir disto, a comunidade científica americana (15) condenou a técnica e propôs a necessidade de mais estudos sobre o uso de tecido adiposo para enxertia mamária, hipotizando que os adipócitos poderiam estimular a formação de câncer nas mamas, juntamente com a preocupação de que o aparecimento de calcificação no pós-operatório poderia afetar a prevenção e o seguimento pós-operatório desta neoplasia. Portanto, na década de 1990, enquanto o enxerto de gordura em todas as regiões corporais ganhava grande popularidade, a lipoescultura mamária passava a ser um procedimento proscrito. Coleman (16-17), entre o final da década de 90 e início dos anos 2000, padronizou a forma de preparo e aplicação da lipoenxertia utilizando o conceito de microenxertia por microtúneis e denominou a técnica como de enxerto estruturado de gordura, mostrando resultados bons e reproduzíveis.

Com a viabilidade e a previsibilidade alcançadas com o emprego da técnica de lipoenxertia estruturada de gordura, associada aos bons resultados publicados em grandes séries de casos, na primeira década dos anos 2000 (18,19), e ainda somado à melhor interpretação e padronização dos achados radiológicos propostos pelo Colégio Americano de Radiologia (ACR), a Sociedade Americana de Cirurgia Plástica (20) deixou de condenar a utilização de tecido adiposo em região mamária pela ausência de evidências científicas e clínicas de seu potencial maléfico, como previamente sugerido (15). A partir de então, o uso de células de gordura como material de preenchimento e reconstrução mamária passou a despertar novo interesse, ressurgindo como promissor; entretanto, ainda cercado de dúvidas quanto às suas indicações e à sua segurança para a prática clínica.

Alguns estudos publicados, nos últimos dez anos, procuram mostrar a segurança do procedimento em relação às complicações clínicas e ao risco oncológico. Considerando estes fatos, objetivou-se reunir informações e identificar, por meio de revisão sistemática, as indicações do procedimento e a sua segurança, por relatos das complicações clínicas, as alterações radiológicas e a incidência de câncer de mama, primário ou recidivado, nas mulheres tratadas com lipoenxertia na topografia da mama.

Acredita-se que, desta forma, será possível auxiliar os profissionais que buscam novas opções cirúrgicas para tratamento estético e reparador das mamas.

2. Objetivos

2.1. Objetivo geral

Avaliar as indicações da lipoenxertia autóloga na topografia de mama feminina e a segurança do procedimento por meio de uma revisão sistemática.

2.2. Objetivos específicos

- Avaliar as indicações da lipoenxertia autóloga na topografia de mama feminina.
- Avaliar a segurança do procedimento quanto às complicações clínicas.
- Avaliar a segurança do procedimento quanto às alterações radiológicas.
- Avaliar o risco oncológico para o câncer de mama.

3. Publicação

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Clinical applicability and safety of autologous fat grafting to the female breast: a systematic review

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Abstract

Background: Autologous fat grafting to the breast for cosmetic and reconstructive purposes is still controversial regarding its safety and efficacy. The objective of this study was to conduct a systematic review on clinical applicability and safety of the technique. **Methods:** An online search of the Cochrane Library, MEDLINE, EMBASE and SCIELO was conducted from July 1986 to June 2011. Studies included original articles of autologous liposuctioned fat grafting to the female breast with description of clinical complications and/or radiographic changes and/or local breast cancer recurrence. **Results:** This review included 60 articles with 4739 patients. Thirty studies used fat grafting for augmentation and 41 for reconstructive procedures. The incidence of clinical complications identified in 21 studies was 64/3015, the majority of them were induration and/or palpable nodulation. Radiographic changes were 266/2560 in 17 studies; more than 50% of them were consistent with cysts. The local recurrence of breast cancer (14/616) was evaluated in three studies, which only one is prospective and none is randomized. **Conclusion:** A broad clinical applicability of the procedure was identified. Complication rate was low and there was no evidence of interference with breast cancer detection. Study results concerning oncological risk are not clear at present.

Introduction

The transfer of autologous fat in surgical reconstruction dates back to the end of the nineteenth century. In 1893, Neuber described the procedure after implanting a small piece of upper arm fat tissue to correct a scar depression in the face^{1,2}. Since then, fat tissue has been employed for the correction of multiple body deformities^{3,4} and has been reported to be the source of the first breast reconstruction. In 1895, Czerny^{5,6} used a large lipoma from the dorsal flank of a patient for breast reconstruction after excision of a benign lesion.

With the advent of liposuction in the seventies of the XX century, the suctioned fat that would be discharged started to be injected in bolus without any preparation by plastic surgeons^{7,8}. Since then, the fat grafting began to be widely used also in gynaecological; urological; neurological; orthopaedic; ear, nose and throat; trauma; and thoracic surgeries. It proved to be efficient for correcting deformities in virtually all body areas and also in its use for cosmetic procedures^{3,4,9,10}. However, during the seventies and eighties, unlike in other body areas, aesthetic and reconstructive results in the breast were not satisfactory, in addition to the appearance of many complications^{11,12}.

Furthermore, it was hypothesized that adipocytes could stimulate the formation of breast cancer and radiographic changes in the postoperative period. This could compromise the detection of a future potentially malignant lesion. In 1987, the American Society of Plastic Surgery¹³ prohibited the use of autologous fat grafting to the female breast.

In the nineties, Coleman formulated new concepts standardizing the structural fat grafting technique^{14,15}. Fat grafting then became a therapeutic method used

in various surgical specialties with cosmetic and reparative purposes. However, fat grafting to the breast continued to be a prohibited procedure¹³.

Differently from other areas of the body, in the breast, adipocytes are implanted in a poorly vascularized and loose region. Therefore, the fat grafting demands greater contact with the receptor tissue, to ensure adequate nutrition and immobilization for adipocytes survival in the first days, prior to their integration. Such anatomical characteristics of the breast, justify the poor results and high rate of complications, compared to other body topographies, which has been observed when the procedure is performed without the structural fat grafting concept. Although it has been used by few authors since earlier eighties^{10,16-19}, the technique was standardized by Coleman only in 1995¹⁴. This concept advocates that the fat must be grafted in small amounts by multiple tunnels, design in many layers and directions, so that the largest possible number of adipocytes could be in contact with the receptor site and, thus can receive adequate nutrition for their survival. Thin cannulas (1.2-3mm) and syringes of low volume (1-20ml) allow for greater accuracy of the grafted amount per tunnel, avoiding the bolus injection. This concept was able to address the unacceptable rate of fat grafting complications in the breast, previously reported. These complications are secondary to the death of fat cells, which undergo a process of lipolysis with subsequent release of lipids and proteins. When this necrotic tissue is not completely absorbed by the body, an inflammatory process takes place resulting in fibrosis and/or cystic formation, with or without calcification, and also local infection²⁰⁻²³.

In the second half of the first decade of 2000, some case series adopting the structural fat grafting to the breast were published reporting good results^{16,17,24}.

Therefore, a renewed interest in the procedure arose with these articles. However, fat grafting still raises doubts as to its indication and safety in clinical practice. During the last ten years, after some published studies have attempted to demonstrate the safety of the structural fat grafting to the breast in terms of clinical complications and oncological risk, the American Society of Plastic Surgery in 2009, failed to prohibit the procedure due to lack of evidence, although they do not recommend it²⁵.

Our objective is to gather information, identify the indications and safety of the procedure, using a systematic review of clinical complications, radiographic changes and incidence of breast cancer (primary or recurrent) in patients treated with fat grafting to the breast.

Methods

Search Strategy

A systematic review of autologous fat grafting to the female breast was conducted according to the guidelines in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)²⁶. The search for articles published in the last 25 years (from July 1986 to June 2011), was independently carried out by two reviewers after accessing the electronic databases of "The Cochrane Library", U.S. National Library of Medicine (MEDLINE), EMBASE and Scientific Electronic Library Online (SciELO). Appropriate keywords in the English language were combined by Boolean logical operators, as follows: "fat autografting" OR "fat grafting" OR "fat autograft" OR "fat graft" OR "fat transplantation" OR "fat Injection" OR "autologous fat" OR "lipostructuring" OR

"lipotransfer" OR "lipomodelling" OR "lipomodeling" AND "breast", adapted to the appropriate syntax of each database. Studies that were considered as potentially relevant according to titles were cross-referenced in search of additional articles of potential interest, with no restriction to language, type of study or publication media.

Inclusion Criteria

Original articles of autologous fat grafting to the human female breast with fat recently removed by liposuction, independent of the presence of mammary gland were eligible for this study.

In this review, only articles that mentioned results such as clinical complications and/or radiographic changes and/or incidence of breast cancer in patients treated with the previously described technique were included.

Exclusion Criteria

Duplicate articles or repeated casuistic were excluded. Studies using recently suctioned mature adipocytes in a proportion lower than 50%, characterizing stem cell implants, as well as those that did not contain description of the indication for the procedure were not considered eligible for this review. In addition, articles without original data cases, such as reviews or simple technique descriptions were also ineligible.

Study selection

Abstracts of studies initially selected were then evaluated by all the four independent reviewers to determine eligibility. In this case the full-text of articles

were retrieved for reading, evaluating, data extraction and inclusion in the systematic review. When a selected study was not completely available to the reviewers in the electronic media or local libraries, the authors of this article²⁷ were contacted by e-mail to request it in its entirety.

Extraction of data results

Data from studies, including authors, date of publication, number of subjects, indication for the procedure, type of study, technique used for adipocyte implantation, time of follow-up, efficacy of treatment, occurrence of clinical complications, radiographic changes, incidence of primary and recurrent breast cancer, were independently extracted and tabulated by two reviewers. Possible discrepancies were discussed and reviewed by all the four reviewers until agreement among them.

In clinical trial articles and observational cohort studies, case controls and case series with more than 20 patients, the outcomes of interest previously defined were indication; efficacy; incidence of clinical complications, radiological changes and breast cancer. Although efficacy was described in a subjective and widely heterogeneous way among the studies, it was presented according to the original authors' assessment. Studies of case reports and case series with up to 20 patients, because the likelihood of bias due to the influence of a learning curve on the results and low volume for evaluation of breast cancer incidence were used only as an additional source for the description of indications, type of complications and radiographic changes and their respective prevalence rates, but were excluded from the assessment of the incidence of clinical complications, radiographic changes or breast cancer.

Assessment of study quality

The methodological quality of the studies was also assessed by two independent reviewers regarding level of evidence and grade of recommendation according to the criteria of Oxford Centre for Evidence-Based Medicine²⁸, and GRADE (Grading of Recommendation Assessment, Development and Evaluation)²⁹. Observational studies and clinical trials lacking a detailed description of the randomization procedure were considered to have a high potential for biases³⁰⁻³².

Statistical analysis

Outcomes of interest were tabulated, organized and shown in a descriptive and individual form, considering the methodological quality of each study. The prevalence rates of clinical complications and radiological changes were identified. A meta-analysis was not performed due to the wide range of heterogeneous methodology among studies³⁰⁻³².

Results

A database search for the pre specified keywords identified 302 articles (171 in EMBASE, 131 in MEDLINE and none in Cochrane Library and SciELO). After the exclusion of duplicate articles and manual cross-referencing to the previously identified articles, two new articles were included^{33,34}, with a total of 95 articles. Of these, 23 articles were excluded after reading the abstracts due to inadequate studies for the review. Seventy-two studies were then eligible for full-text reading. Among them, one was excluded for using fat block transplantation instead of liposuction³⁵, two for using more than 50% of immature adipocytes,

which characterizes stem cell transplant^{36,37}, two for failing to represent numbers regarding the outcomes of interest^{38,39} and seven for showing apparently repeat case studies⁴⁰⁻⁴⁶. Therefore, 60 articles (totalling 4739 women) remained and were used for this systematic review. Only 27 articles were assessed for incidence of clinical complications and/or radiological findings and/or breast cancer (Figure 1). Of these, 21 studies with 3015 women were used to extract the incidence of clinical complications, 17 studies with 2560 patients were used to extract the incidence of radiographic changes and three studies with 616 women were used to evaluate the oncological risk of local recurrence of breast cancer.

There were 57 observational studies. Thirty-six of these studies were represented by case reports and case series. Seven were retrospective cohort studies, twelve were prospective cohort studies, one was a diagnostic validation cohort study and one was a case-control study. Three studies were clinical trials without descriptions of randomization. The methodology and quality of each study are represented in Table 1.

Clinical Applicability

There were identified 30 studies with at least 928 patients that used fat grafting to the breast for aesthetic augmentation and 41 studies with more than 1888 patients that used the procedure for reconstructive purposes. The majority of these articles are considered as being of very low and low quality according to GRADE criteria. In general, the procedure was reported as being satisfactory (Table 1).

Specific clinical indications for autologous fat grafting to the breast according to the GRADE criteria for methodological quality are illustrated in Figure 2. In

aesthetic field, the main indication for the procedure was primary aesthetic breast augmentation reported in 30 studies covering about 1000 women, followed by secondary aesthetic augmentation after removal of the alloplastic implant, and use of the technique as complementation to improve the contour and shape of the breasts after placement of the alloplastic implant. All studies investigating these indications were observational. Most consisted of case reports and case series, showing a very low and low quality of methodology according to GRADE criteria. In reconstructive field, the procedure was mainly indicated for partial breast reconstruction and/or correction of breast deformities, its second most frequent indication (15 studies, totalling more than 500 cases), followed by total breast reconstruction within its different techniques. As treatment of congenital breast deformities, the autologous fat graft was used in Poland's syndrome, being its fifth main indication (10 studies, totalling more than 60 patients) and tuberous breasts. Furthermore, in more recent studies (starting in 2009), autologous fat grafting has been reported as therapy for post-radiotherapy radiodermatitis^{67,85} and as treatment of capsular contracture in breasts with alloplastic implants⁸² (Figure 2).

Safety

Clinical complications

Initially, all the 60 studies were assessed for the clinical complications, it were identified in 155 of 4739 patients. Among them, nodulation and/or induration was identified in 93 cases (60%), follow by deep infection, in 19 patients (12%). There was no report of death. Three cases of sepsis were identified in studies of case reports of complications, which the structured fat grafting was not described

(Figure 3). In one of these cases, the patient received fat grafting to the breasts and buttocks. She developed abscesses in one breast and in one gluteal region, requiring open drainage for both regions³³.

Considering the 21 studies with better methodological quality, which described a given time of follow-up, standardized technique and more than 20 patients, the incidence of clinical complications was 64 in 3015 cases (2,12%), as illustrated in Table 2. Among them, the most serious complication reported was pneumothorax (Figure 3).

Radiographic changes

Concerning the 299 radiological abnormal findings identified on mammography (MMG) in the postoperative follow-up, about $\frac{3}{4}$ were images consistent with cysts, while in 13% of cases they were consistent with microcalcifications. On Ultrasound, about 89% of the 331 radiographic changes described corresponded to images consistent with cyst and/or liponecrotic cysts. Magnetic Resonance Imaging (MRI) also showed images that were consistent with cysts or liponecrotic cysts in 65% of the 46 findings identified and with nodulation in 35% of them (Figure 4). The overall occurrence of radiological findings was 266 cases in 2560 patients (10,39%). The descriptions of radiographic changes in each study are illustrated in Table 3.

Breast cancer risk

Of the 3 studies evaluating 616 patients (mean follow-up period of 45.17 months) that were used to identify the oncological risk of local recurrence of breast

cancer in cases treated with breast fat grafting, 14 cases were described (2,27%). In all these cases, the patients had undergone mastectomy for breast cancer treatment (Table 4). There was no report of the incidence of primary breast cancer.

Discussion

This systematic review was performed with information from different studies using a wide range of heterogeneous methods. The majority of these studies had a low grade of recommendation, with a likelihood of bias³⁰⁻³². Despite these difficulties and some limitations, after organization and assessment of the results, the authors believe it was possible to demonstrate the relative safety of autologous fat grafting to the female breast with fat removed by recent liposuction for the aesthetic and reconstructive treatment of diverse breast disorders.

Although some studies used in this review mentioned, where in the body the fat was harvested and/or the method for its preparation, we have not considered such information relevant, because previous articles that aimed to evaluate them, have not found any influence in the outcomes⁹⁶⁻¹⁰⁰. The fat grafting is usually harvested from the abdomen, hip and inner thigh, due to the great amount of adipocytes in these topographies. Most authors prefer, as a method of preparation, to centrifuge the liposuctioned material at 3000 rpm for 3 minutes, because it is believed to be faster and give a higher adipocyte concentration in the graft, allowing greater predictability in the outcome.

The technique was mainly indicated for aesthetic breast augmentation in 30 of the 60 articles used in this review. Despite the high efficacy reported by the majority of the authors, all articles were observational and mostly consisted

of case reports and case series. Not enough data was provided to be compared with other methods for a more accurate assessment of the results. Meanwhile, a registered prospective clinical trial has been running aiming to compare the results of SFG with implant augmentation (A Prospective Study of Autologous Fat Grafting for Breast Augmentation, clinicaltrials.gov ID: NCT00663156).

In the field of breast reconstruction, similar to the previously cited indication, the articles were also observational and descriptive in design. However, these articles allowed us to identify that fat grafting may be applied alone in total and partial reconstructions with usually more than one application session. It may also be used in association with myocutaneous flaps such as the TRAM (transverse *rectus abdominis* myocutaneous flap), *latissimus dorsi* muscle flap or even free microsurgical flaps to improve breast shape and volume. Fat grafting may be associated with alloplastic implants to complement and improve the shape and final volume of the reconstructed breast. Concerning clinical application, some studies have reported that the use of fat grafting technique prepares the recipient site for subsequent alloplastic implants in women with thin subcutaneous tissue or previously irradiated skin.

In a non-randomized clinical trial, Panetiere *et al.*⁶⁷ observed a significant reduction in referred pain, atrophy and fibrosis among other changes in patients with irradiated breasts and those reconstructed with breast implants and fat grafting, in comparison to those who did not receive fat grafting. Improvement in severe radiodermatitis lesions was described, such as ulcer healing and regeneration of fibrotic areas in breasts receiving fat grafting^{36,67,85}. Retrospective cohort studies, large case series and some reports described satisfactory results with the use of

autologous fat grafting for the correction of congenital deformities such as Poland's syndrome and Tuberous Breast.

With the purpose of increasing the likelihood of identifying all the possible and worst clinical related complications, there were included all studies reporting such complications. In this review, the authors found 155 cases of complications among 4739 women treated with breast fat grafting in the 60 studies identified. Sixty per cent of these complications were represented by breast mass and/or induration, disorders of low morbidity and commonly reported after any breast procedure performed. It is worth mentioning that autologous breast fat grafting uses the patient's own tissue. The immune response is not elicited and extrusion is lacking. Furthermore, no replacement is needed, making the procedure safe, when compared to conventional techniques for aesthetic breast augmentation or reconstruction. Three cases of sepsis were identified^{33,49,88}, accounting for the most severe complications reported. The authors who described these cases had not performed the procedure or described the technique employed. These cases had a high likelihood of occurring probably because bolus liposuction was performed and not structural fat grafting that is currently recommended for implantation of adipocytes.

In this review, the occurrence and severity of clinical complications resulting from autologous fat grafting were lower than those described in breast cosmetic and reconstruction procedures performed with breast implants and/or myocutaneous flaps¹⁰¹⁻¹¹³. However, its use is still controversial among plastic surgeons, radiologists, oncologists and breast surgeons. Some specialists believe that masses and palpable nodes, responsible for approximately 60% of all clinical

complications identified, could interfere with future breast cancer screening, in addition to generating great psychological discomfort among patients.

Studies with criticism directed at the procedure and emphasizing difficulties in radiological control after autologous fat grafting to the breast are usually case reports and case series without description of the technique used in the procedure. These articles had a low level of evidence, according to criteria of Oxford Centre for Evidence-Based Medicine²⁸ and very low level of methodological quality by GRADE criteria²⁹. Seventeen articles totalling 2707 patients were identified and used to assess the occurrence of abnormal radiographic changes. Although classified, in its majority and at least as “low” by GRADE, these articles report the technique used and follow-up time after fat grafting. The incidence of radiographic changes described was similar to that of other breast procedures performed^{52,57}. In 2011, a study by Veber *et al.*⁷⁸ using a diagnostic validation cohort (level of evidence 1B, Grade A of recommendation by the "Oxford Centre for Evidence-Based Medicine" and considered “high” by GRADE criteria) compared mammograms performed before and after autologous fat grafting to the breast. Those authors observed that one year after the procedure, there was an improvement in radiological pattern, according to criteria of the “Breast Imaging Reporting and Data System” (BI-RADS) of the American College of Radiology, concluding that fat grafting to the breast did not cause additional difficulties in differentiating a suspected radiological change⁷⁸. Some authors indicate a biopsy in case of doubt or when glandular changes are consistent with BI-RADS III classification⁶¹. However, it is important to emphasize that the method was most widely applied in aesthetic augmentation, performed mostly in young women without imaging follow-up.

Concerning the risk of breast cancer, theories based on experimental studies in the scientific environment have reported that recently grafted adipocytes and preadipocytes (representing around 10% of fat cells in the lipoaspirate) have a carcinogenic potential¹⁰⁸⁻¹¹². These theories are based on a higher local concentration of oestrogen resulting from aromatases derived from adipocytes and some adipocytokines released from these cells that can stimulate angiogenesis and induce cancer^{113,114}. Nevertheless, in a recent systematic review of experimental studies on the subject, Lohsiriwat *et al.*¹¹³ did not observe a conclusive effect on breast cancer.

Of all the studies included in this review, only three showed results that enabled us to assess oncological risk. Although the remaining studies did not mention any incidence of primary cancer or refer to a low recurrence rate, they lacked appropriate patient homogeneity, study method and follow-up period that allowed us to make this type of analysis. Of the three studies used to assess oncological risk, a prospective cohort study by Rietjens *et al.*⁸⁴ with a follow-up period of approximately 18 months analysed the recurrence risk for patients treated for breast cancer in 114 total mastectomies and 77 partial mastectomies with breast fat grafting. Those authors identified recurrence in one of the 191 breasts treated in 158 patients and considered that the recurrence was not directly influenced by fat grafting because it appeared shortly after the procedure, revealing a low rate of recurrence. However, the number of patients evaluated was small and the follow-up period was very short to assess oncological risk. The lack of a control group and heterogeneity of treated cases may also compromise appropriate scientific basis on the data shown, since

patients undergoing partial mastectomy could have a higher recurrence risk than those who had complete resection of the breast.

In a non-randomized clinical trial, Rigotti *et al.*⁷⁵ assessed the incidence of tumour recurrence in patients treated for breast cancer with modified radical mastectomy and autologous fat grafting for breast reconstruction. Breast cancer recurred in 5 of the 137 patients treated. The authors described that there was no higher oncological risk in patients treated with lipofilling than in the control group. A criticism levelled at the study was the method of patient allocation. In addition, the control group was not independent from the cases and the study was not carried out simultaneously.

Finally, the study with the best methodological quality and therefore with the highest level of evidence was published by Petit *et al.*⁹⁵ These authors conducted a case-control study, in which 321 patients were compared and matched to 642 women with homogeneous characteristics who received the same oncological treatment during a mean period of 26 months. The eight cases of local recurrences reported in the lipofilling group did not qualify as a higher risk of tumour recurrence, when compared to 19 cases of recurrences described in the controls, as reported by the authors. This study obtained the most extensive evidence of safety regarding the oncological risk of lipofilling. However, a limitation was that it was not a prospective randomized controlled clinical trial. Therefore, in this review the rate of breast cancer recurrence in studies describing this complication was similar to that shown in the literature in patients undergoing mastectomy who did not receive breast fat grafting¹¹⁵⁻¹¹⁹.

Beyond these articles, a clinical trial that has just been completed was identified. When published, it may bring some additional answers about fat grafting safety in the breast (RESTORE-2, clinicaltrials.gov ID: NNCT00616135). Therefore, although at present there is no evidence that clinically, fat grafting increases the risk of breast cancer^{25,75,84,95}, its oncological safety is not yet clear.

In conclusion, there is a broad clinical applicability for autologous fat grafting to the breast, in the cosmetic and reconstructive field, when it is performed within the structured concept. In the future, hopefully it could be used as an additional therapeutic procedure for some diseases, such as radiodermatitis, capsular contracture, among others. When the procedure is performed and the patients have a close follow-up by experient teams, the complication rate was low with no evidence of interference in breast cancer detection. Concerning the oncological risk of breast cancer, in this review only three studies that have looked at oncological recurrence. Among them, only one is prospective and none is randomised, indicating that oncological safety is not clear at present. Thus, it is concluded that further studies are necessary, particularly randomized controlled trials with long follow-up time, to verify new clinical indications and to evaluate the safety of the procedure in terms of oncological risk.

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Table 1. Characteristics of included studies

Reference	Year	Study Design	GRADE*	Fat Graft for Cosmetic Augmentation: Number of Patients (breasts)	Fat Graft for Reconstructive Treatment: Number of Patients (breasts)	Efficacy
Bircoll ¹⁸	1987	Case Report	Very low	1(2)	-	Satisfactory
Bircoll and Novack ¹⁹	1987	Case Report	Very low	-	1(1)	Satisfactory
Hori <i>et al.</i> ¹¹	1989	Case Report	Very low	1(2)	-	RCC
Maillard ¹²	1994	Case Report	Very low	1(2)	-	RCC
Uchiyama <i>et al.</i> ⁴⁷	2000	Case Report	Very low	3(6)	-	RAR
Cheung <i>et al.</i> ⁴⁸	2000	Case Report	Very low	1(2)	-	RAR
Valdatta <i>et al.</i> ⁴⁹	2001	Case Report	Very low	1(2)	-	RCC
Gulsun <i>et al.</i> ⁵⁰	2003	Case Report	Very low	1(2)	-	RAR
Kwak <i>et al.</i> ⁵¹	2004	Case Report	Very low	1(2)	-	RAR
Spear <i>et al.</i> ²⁴	2005	Retrospective Cohort	Low	-	43	Satisfactory
Pierrefeu-Lagrange <i>et al.</i> ⁵²	2006	Case Series	Low	-	30 (34)	Satisfactory
Pulagam <i>et al.</i> ⁵³	2006	Case Report	Very low	1(2)	1(1)	RAR
Coleman and Saboeiro ⁶	2007	Retrospective Cohort	Low	10 (20)	17 (31)	Satisfactory
Missana <i>et al.</i> ⁵⁴	2007	Retrospective Cohort	Low	-	74	Satisfactory
Yoshimura <i>et al.</i> ⁵⁵	2007	Retrospective Cohort	Low	40 (80)	-	Satisfactory
Cotrufo <i>et al.</i> ⁵⁶	2008	Case Series	Low	-	42	Satisfactory
Gosset <i>et al.</i> ⁵⁷	2008	Case Series	Low	-	21	Satisfactory
Pinsolle <i>et al.</i> ⁵⁸	2008	Case Series	Low	-	7	Satisfactory
Mojallal <i>et al.</i> ²⁷	2008	Case Report	Very low	-	1	Satisfactory
Zheng <i>et al.</i> ⁵⁹	2008	Case Series	Low	47	66	Satisfactory
Zocchi and Zulliani ⁶⁰	2008	Retrospective Cohort	Low	181 (326)	-	Satisfactory
Carvajal and Patiño ⁶¹	2008	Case Series	Low	20 (40)	-	RAR
Wang <i>et al.</i> ⁶²	2008	Case Series	Low	33 (66)	-	RAR
Kaufman <i>et al.</i> ⁶³	2009	Prospective Cohort	Low	-	9 (9)	Satisfactory
ELFadl <i>et al.</i> ⁶⁴	2009	Prospective Cohort	Low	1	21	Satisfactory
Delaporte <i>et al.</i> ⁶⁵	2009	Prospective Cohort	Low	-	15 (15)	Satisfactory
Hyakusoku <i>et al.</i> ⁶⁶	2009	Case Series	Low	12 (24)	-	RCC
Panettiere <i>et al.</i> ⁶⁸	2009	Clinical trial	Moderate	-	22 (22)	Satisfactory
Kanchwala <i>et al.</i> ⁶⁸	2009	Retrospective Cohort	Low	-	109	Satisfactory
Del Vecchio ⁶⁹	2009	Case Report	Very low	1 (2)	-	Satisfactory
Salgarello <i>et al.</i> ⁷⁰	2009	Case Report	Very low	-	2 (2)	Satisfactory
Mu <i>et al.</i> ⁷¹	2009	Case Series	Very low	17 (34)	-	RCC
Pereira and Sterodimas ⁷²	2009	Case Report	Very low	-	1 (2)	Satisfactory
Lazaretti ⁷³	2009	Case Report	Very low	1 (2)	-	RCC
Delay <i>et al.</i> ¹⁷	2009	Case Series	Low	30	850	Satisfactory
Illouz and Sterodimas ¹⁶	2009	Case Series	Low	385 (770)	435 (478)	Satisfactory
Babovic ⁷⁴	2010	Case Report	Very low	-	1 (1)	Satisfactory
Rigotti <i>et al.</i> ⁷⁵	2010	Clinical Trial	Moderate	-	911	Satisfactory
Serra-Renom <i>et al.</i> ⁷⁶	2010	Case Series	Low	-	65 (65)	Satisfactory
Erol <i>et al.</i> ⁷⁷	2010	Case Report	Very low	1 (2)	1 (1)	RCC
Veber <i>et al.</i> ⁷⁸	2010	Diagnostic Validation Cohort	Moderate	44	32	Satisfactory
Talbot <i>et al.</i> ³³	2010	Case Report	Very low	1 (2)	-	RCC
Wang <i>et al.</i> ⁷⁹	2010	Prospective Cohort	Low	41 (82)	-	RAR
Irani <i>et al.</i> ⁸⁰	2010	Retrospective Cohort	Low	-	25 (25)	Satisfactory
Villani <i>et al.</i> ⁸¹	2010	Case Series	Low	-	5 (5)	Satisfactory
Ueberreiter <i>et al.</i> ⁸²	2010	Prospective Cohort	Low	52 (104)	33	Satisfactory
Del Vecchio and Bucky ⁶³	2011	Prospective Cohort	Low	NS	NS	Satisfactory
Pettus <i>et al.</i> ³⁴	2011	Case Report	Very low	-	1 (2)	RAR
Rietjens <i>et al.</i> ⁸⁴	2011	Prospective Cohort	Low	1 (2)	(192)	Satisfactory
Panettiere <i>et al.</i> ⁸⁵	2011	Case Report	Very low	-	1 (2)	Satisfactory
Serra-Renom <i>et al.</i> ⁸⁶	2011	Prospective Cohort	Low	-	28 (56)	Satisfactory
Serra-Renom <i>et al.</i> ⁸⁷	2011	Prospective Cohort	Low	-	8 (9)	Satisfactory
Lee <i>et al.</i> ⁸⁸	2011	Case Report	Very low	1 (2)	-	RCC
Sarfati <i>et al.</i> ⁸⁹	2011	Prospective Cohort	Low	-	28	Satisfactory
Losken <i>et al.</i> ⁹⁰	2011	Case Series	Low	-	107	Satisfactory
Yang and Lee ⁹¹	2011	Case Report	Very low	-	1 (1)	Satisfactory
Beck <i>et al.</i> ⁹²	2011	Prospective Cohort	Low	-	10	Satisfactory
Yong <i>et al.</i> ⁹³	2011	Case Series	Low	-	100 (130)	Satisfactory
Murphy <i>et al.</i> ⁹⁴	2011	Prospective Cohort	Low	-	91	Satisfactory
Petit <i>et al.</i> ⁹⁵	2011	Case-Control	Moderate	-	321	NR
Total	60	studies		30 studies 928 + NS patients	41 studies 1888 + NS patients	

RCC=Report of clinical complication; RAR=Report of Radiological Alteration; NR=Not Referred; NS=Authors mentioned clinical applicability, although the amount of patients was not specified.

* Methodological quality according to GRADE classification²³

Table 2. Incidence of clinical complications

Reference	Year	Number of Patients	Technique	Mean Follow-up Time (months)	Clinical Complications
Spear <i>et al.</i> ²⁴	2005	37	Structured Fat Graft	15	3/37
Missana <i>et al.</i> ⁵⁴	2007	69	Structured Fat Graft	12	0
Yoshimura <i>et al.</i> ⁵⁵	2007	40	Structured Fat Graft	6	0
Cotrufo <i>et al.</i> ⁵⁶	2008	42	Structured Fat Graft	7	1/42
Zheng <i>et al.</i> ⁵⁹	2008	66	Structured Fat Graft	37	1/66
Zocchi and Zulliani ⁶⁰	2008	181	Structured Fat Graft	12	19/181
Wang <i>et al.</i> ⁶²	2008	33	Non-Structured Fat Graft	3	14/33
ELFadl <i>et al.</i> ⁶⁴	2009	22	Structured Fat Graft	5	2/22
Kanchwala <i>et al.</i> ⁶⁸	2009	110	Structured Fat Graft	21	0
Delay <i>et al.</i> ¹⁷	2009	880	Structured Fat Graft	12	35/880
Illouz and Sterodimas ¹⁶	2009	820	Structured Fat Graft	12	17/820
Serra-Renom <i>et al.</i> ⁷⁶	2010	65	Structured Fat Graft	12	0
Irani <i>et al.</i> ⁸⁰	2010	25	Structured Fat Graft	6	2/25
Ueberreiter <i>et al.</i> ⁸²	2010	85	Structured Fat Graft	6	2/85
Del Vecchio and Bucky ⁸³	2011	25	Structured Fat Graft	6	0
Rietjens <i>et al.</i> ⁸⁴	2011	158	Structured Fat Graft	18.3	7/158
Serra-Renom <i>et al.</i> ⁸⁶	2011	28	Structured Fat Graft	12	0
Sarfati <i>et al.</i> ⁸⁹	2011	22	Structured Fat Graft	17	0
Losken <i>et al.</i> ⁹⁰	2011	107	Structured Fat Graft	8	12/107
Yong <i>et al.</i> ⁹³	2011	100	Structured Fat Graft	8	2/100
Murphy <i>et al.</i> ⁹⁴	2011	100	Structured Fat Graft	NR	0
Total	21 Studies	3015		12.35	64/3015

Table 3. Incidence of radiographic changes

Reference	Year	Number of Patients	Technique	Mean Follow-up Time (months)	Radiological changes
Pierrefeu-Lagrange <i>et al.</i> ⁵²	2006	30	Structured Fat Graft	12	12/30
Missana <i>et al.</i> ⁵⁴	2007	69	Structured Fat Graft	12	5/69
Yoshimura <i>et al.</i> ⁵⁵	2007	40	Structured Fat Graft	6	2/40
Gosset <i>et al.</i> ⁵⁷	2008	21	Structured Fat Graft	12	18/21
Zheng <i>et al.</i> ⁵⁹	2008	66	Structured Fat Graft	37	11/66
Zocchi and Zulliani ⁶⁰	2008	181	Structured Fat Graft	12	7/181
Wang <i>et al.</i> ⁶²	2008	33	Non-Structured Fat Graft	3	14/33
ELFadl <i>et al.</i> ⁶⁴	2009	22	Structured Fat Graft	5	2/22
Delay <i>et al.</i> ¹⁷	2009	880	Structured Fat Graft	12	176/880
Illouz and Sterodimas ¹⁶	2009	820	Structured Fat Graft	12	17/820
Veber <i>et al.</i> ⁷⁸	2010	31	Structured Fat Graft	12	20/31
Wang <i>et al.</i> ⁷⁹	2010	41	Non-Structured Fat Graft	16	34/41
Ueberreiter <i>et al.</i> ⁸²	2010	85	Structured Fat Graft	6	0
Del Vecchio and Bucky ⁸³	2011	25	Structured Fat Graft	6	0
Rietjens <i>et al.</i> ⁸⁴	2011	79	Structured Fat Graft	18.3	4/79
Losken <i>et al.</i> ⁹⁰	2011	107	Structured Fat Graft	8	1/107
Murphy <i>et al.</i> ⁹⁴	2011	30	Structured Fat Graft	NR	9/30
Total	17 studies	2560		12.29	266/2560

Table 4. Assessment of oncological risk (local recurrence)

Reference	Year	Number of Patients	Technique	Mean Follow-up Time (months)	Locoregional Recurrence of Breast Cancer
Rigotti <i>et al.</i> ⁷⁵	2010	137	Structured Fat Graft	91.2	5/137
Rietjens <i>et al.</i> ⁸⁴	2011	158	Structured Fat Graft	18.3	1/158
Petit <i>et al.</i> ⁹⁵	2011	321	Structured Fat Graft	26	8/321
Total	3 studies	616		45.17	14/616

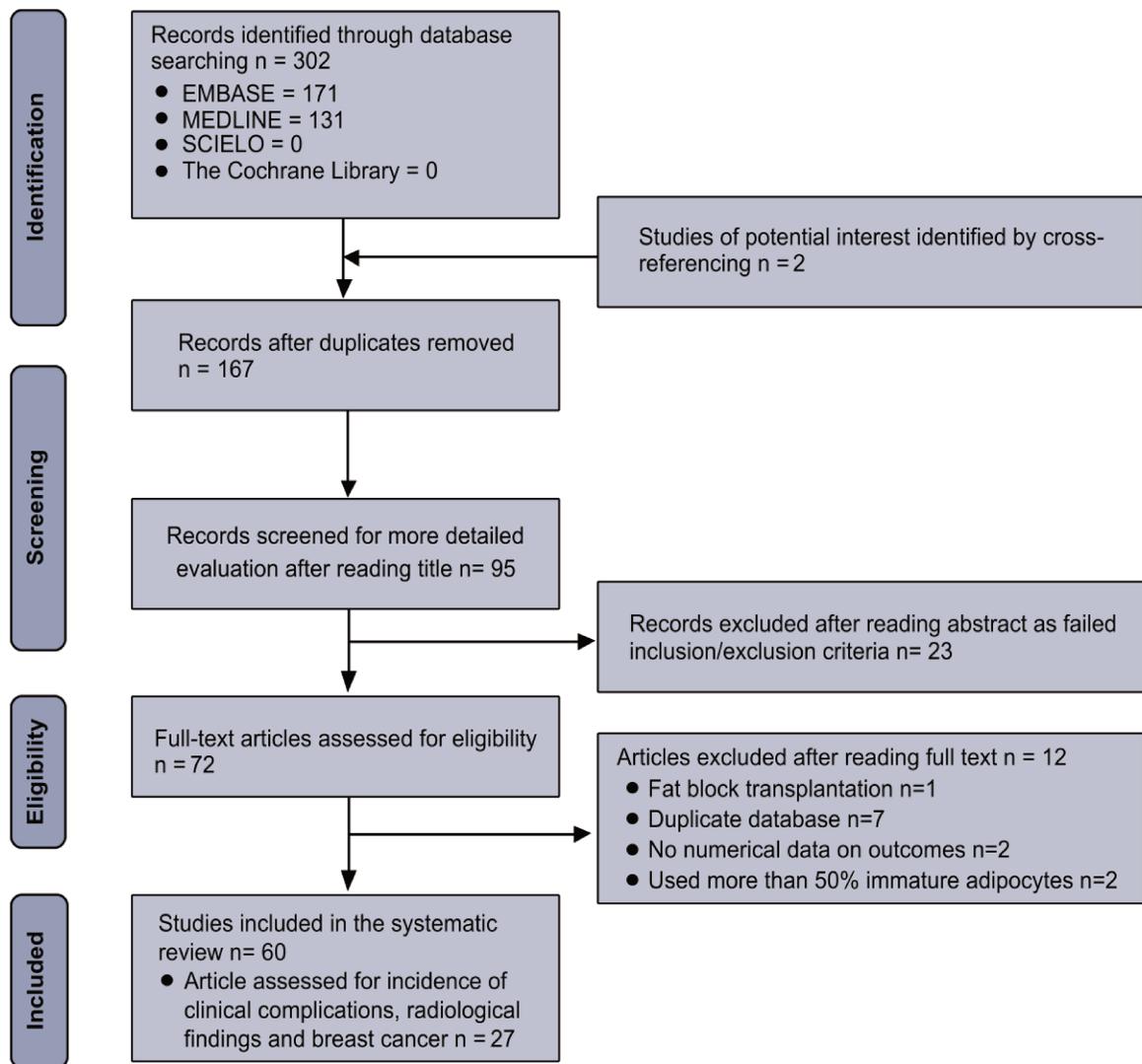


Figura 1. Study Selection (PRISMA diagram for review).

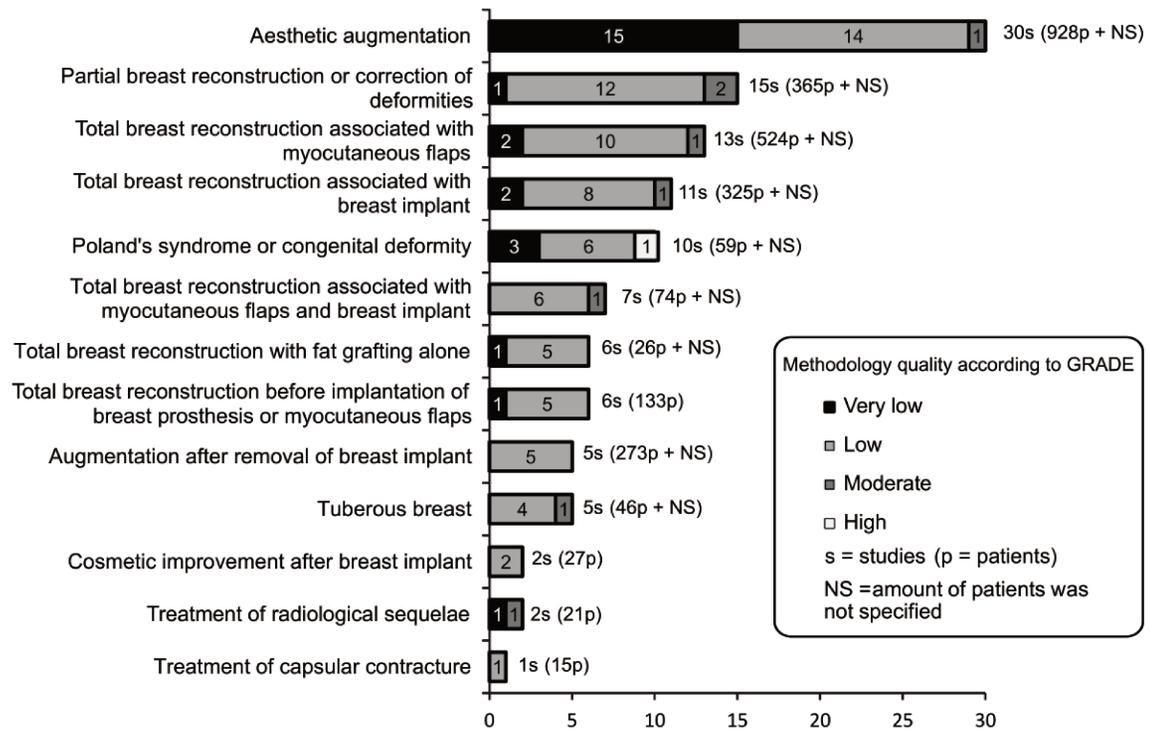


Figura 2. Clinical Indications of autologous fat grafting to the breast associated with the GRADE classification.

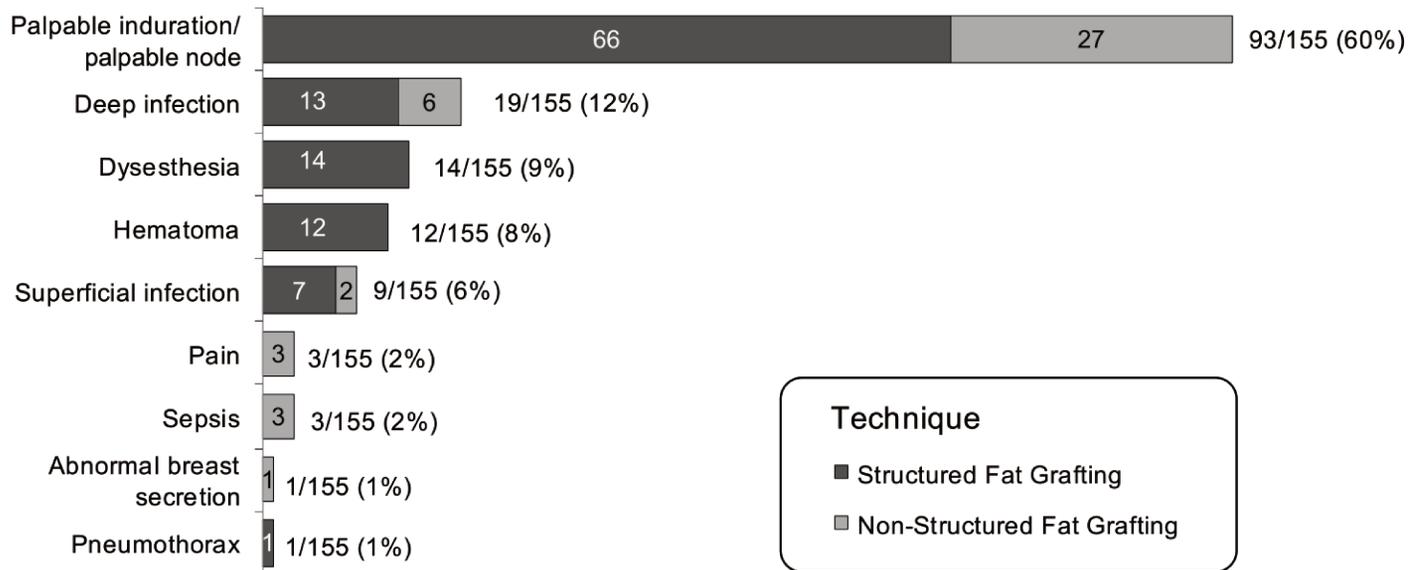


Figure 3. Prevalence among the 155 clinical complications identified in 60 studies according to the technique of fat grafting.

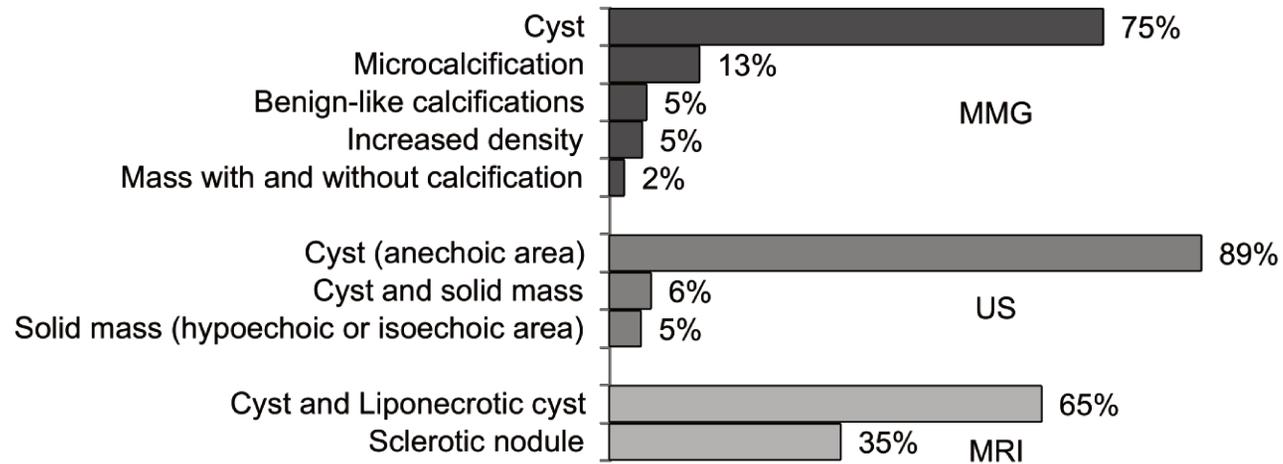


Figure 4. Prevalence of radiological changes identified in 60 studies among the 299 abnormal findings described on mammography (MMG), 331 on ultrasound (US) and 46 on Magnetic Resonance (MRI).

Conflicts of interest

None of the authors have financial interests in any company or institution that might benefit from this publication.

4. Conclusões

- A lipoenxertia mamária é uma técnica promissora para a manipulação das mamas. Na área reconstrutiva, tem aplicação para as deformidades congênitas, como a síndrome de Poland, ou adquiridas, como as sequelas de ressecção mamária parcial e total, pós-traumáticas e patologias mamárias degenerativas. Tem-se observado papel promissor para o tratamento das sequelas de radioterapia. Na área estética, para o tratamento de hipomastia, melhoras do contorno mamário e aumento de volume das mamas, ainda como alternativa aos implantes aloplásticos, com um custo menor e menor índice de rejeição e complicação.
- Nodulações e/ou endurecimentos na região do enxerto foi a principal complicação e correspondeu a mais de 50% das complicações. A infecção profunda, com 12%, foi a segunda complicação mais relatada. Embora as complicações descritas em sua maioria foram de baixa morbidade houve relato de dois casos de sepse, com evolução clínica satisfatória.

- O estudo não identificou interferência entre o procedimento e a investigação preventiva ou acompanhamento pós-operatório do câncer de mama. As alterações radiológicas resultantes da lipoenxertia mamária não representaram dificuldades adicionais na detecção de lesões malignas da mama, quando feita por profissionais qualificados e em conformidade com os critérios do “Breast Imaging Reporting and Data System II” (Bi-RADS II) do Colégio Americano de Radiologia (ACR).
- Quanto ao risco oncológico, devido ao pequeno número de casos e baixo grau de recomendação observado no desenho dos estudos avaliados, os resultados não foram conclusivos, embora aparentemente seguros. Consideramos que existe a necessidade de mais estudos, principalmente ensaios controlados aleatorizados, para confirmar a segurança do procedimento quanto ao risco oncológico.

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