Megavolume Autologous Fat Transfer: Part I. Theory and Principles

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Summary: This article describes the theory and principles behind the authors' success in megavolume (250-ml range) autologous fat transfer to the breasts. When large volumes are grafted into a tight space, the interstitial fluid pressure increases to impair capillary blood flow and the crowded graft droplets coalesce into lakes, with poor graft-to-recipient interface. These factors have historically restricted the volume of fat that can be grafted into small recipient breasts. The decreased interface increases the distance oxygen must diffuse to reach the grafted adipocytes, causing central necrosis to occur before neovascularization. The increased interstitial fluid pressure reduces capillary radius, reducing oxygen delivery to grafted adipose tissue. The Brava external expansion device harnesses the regenerative capabilities of mechanical forces to preoperatively increase the volume and vascularity of the recipient site, allowing megavolumes of fat to be grafted diffusely without significantly decreasing graft-to-recipient interface or increasing interstitial fluid pressure. The application of these principles has allowed the authors to successfully graft megavolumes of fat into the breasts of over 1000 patients with substantial long-term retention. (*Plast. Reconstr. Surg.* 133: 550, 2014.)

"Doctor, can't you just take some from here and put it there?" All plastic surgeons with at least a modest experience in breast surgery have heard these words, and have sadly replied that it was not possible.

We present our theory and principles based on the literature and our personal experience with over 1000 fat-grafting procedures to the breast as evidence of a paradigm shift in the realm of possibilities in surgery. The facts were that we knew of multiple attempts at fat transfer, dating back to the beginning of the twentieth century, and that Chajchir and Benzaquen[1] and Guerrerosantos[2,3] had been grafting liposuctioned fat successfully since the 1980s. However, the fundamentals of realistic large-volume fat grafting for breast augmentation had yet to be determined.

Coleman[4] achieved seemingly miraculous results with small-volume fat transfer in the face and gave us the fundamental principle of "microdroplets" (although we now favor the term, "microribbons") as small units of fat that can survive acute transfer to a subcutaneous bed. Coleman and Saboeiro,[5] Delay et al.,[6] and Rigotti et al.[7] also described experiences with fat grafting the breast, but the capacity to enlarge the breast by more than 200 ml in one stage, or to completely reconstruct a breast after total mastectomy, using fat graft alone, remained an elusive goal whose time had not come.

HISTORY

During the early 1990s, we became intrigued by Ilizarov's demonstrations that when cells were put under stretch, they would sense local strain and respond by proliferating to expand their population and fill the space with tissue.[8,9] Scientists now call this phenomenon mechanotransduction.[10] Lancerotto et al. demonstrated that, in addition to mechanotransduction, force application induces temporary ischemia, which activates the hypoxia-inducible factor 1α/vascular

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endothelial growth factor pathway, inducing angiogenesis.[11] This necessitated a revision of the concept of how tissues might expand through external force application, rather than by means of the traditional internal expanders and has led to the birth of the Brava (Brava, LLC, Miami, Fla.) nonsurgical breast enlargement system.[12] Clinical trials of Brava use without fat grafting showed remarkable success; the findings presented at the meeting of the American Society for Aesthetic Plastic Surgery in 1999 by Dr. Tom Baker resulted in the Best Paper Award.

The initial enthusiasm for Brava without fat grafting as a practical method for breast augmentation eventually began to wane. We typically saw a one-cup bra size long-term maintained enlargement after 3 months of intensive daily use. However, not all patients achieved this result. Poor patient compliance with the device (complicated to wear, though not painful) and slow real tissue growth limited the Brava alternative to very few, highly dedicated patients with much patience.

An early observation of Brava users was that their breasts underwent a marked and temporary enlargement, especially in the initial few days and weeks of application. This rapid expansion was at first thought to be essentially an edematous response of the gross tissue to the novel experience of external expansion. However, magnetic resonance imaging evaluations performed on breasts before and after Brava expansion revealed a startling and optimistic finding—the expanded breasts had a tremendously increased blood supply and an abundantly enlarged fibrovascular scaffold structure, what could be considered the ideal environment for fat engraftment,[13] a finding recently experimentally confirmed by Heit et al.[14] With that happenstance of a somewhat disappointing idea being reevaluated and a new avenue for potential success in breast enlargement being created, it was realized that megavolume fat grafting might be possible.

PRINCIPLES OF GRAFT SURVIVAL

The exploration of this opportunity required us to delve into the knowledge that was extant regarding fat graft survival. Fat grafting is three-dimensional grafting. For the plastic surgeon accustomed to two-dimensional grafting, this is a novel concept with an additional degree of complexity. Based on our extensive clinical experience with megavolume fat-grafting procedures, our literature investigation, and our understanding of fundamental principles of plastic surgery, we advanced the notion that graft retention requires adherence to two fundamental principles: graft-to-recipient interface and interstitial fluid pressure limit.

Graft-to-Recipient Interface

We knew that composite tissue blocks could survive as free nonvascularized grafts if placed in small portions, never exceeding 2 mm in radius.[15–18] The traditional concept of graft survival involved a race between the limited time transplanted cells can survive by plasmatic imbibition and the time it takes for neovascularization to reestablish functional connections between the graft and the recipient capillary network.[18–24] The race is limited to a little more than 2 days, with the fate of the graft hanging in the balance. Because of this 2-mm graft-to-recipient interface limit, no adipocyte should be more than 2 mm away from its recipient capillary network lest it dies before its capillary circulation is restored. This prompted us to consider that only microribbons would survive, whereas larger injections would suffer central necrosis.[17–19,25–28]

We thus realized that we should be delivering droplets of fat through a thin cannula, as microribbons, never exceeding the 2-mm limit. A cylinder with a radius of 0.2 cm has a base with an area of 0.126 cm^2. If we set a conservative limit for the area of the base of the cylinder to be 0.1 cm^2, the maximum volume delivered by a 10-cm-long injection should be 1 cc. This rule is our practical compromise between operative speed and meticulous microdispersion. The several hundred cannula passes should be teased inside the recipient parenchyma as separate microribbons laid down in a three-dimensional pattern of rows that do not overlap or coalesce. We meticulously disperse the graft to avoid coalescence of the droplets into larger collections. We also avoid creating and grafting into cavities—cavity is the enemy, where grafts die and turn into necrotic cysts.

Interstitial Fluid Pressure Limit

Even if we carefully adhere to graft-to-recipient interface constraints, and carefully tease our graft in-between the fibrovascular scaffold of the recipient parenchyma, there is still a major limitation to how much volume a particular block of recipient tissue can accept. As we inject more fat, the recipient site initially enlarges to accommodate the increased volume. The total recipient-site volume is equal to the grafted volume plus the original recipient volume.

However, beyond a certain injection volume, the compliance of tissue rapidly decreases and the

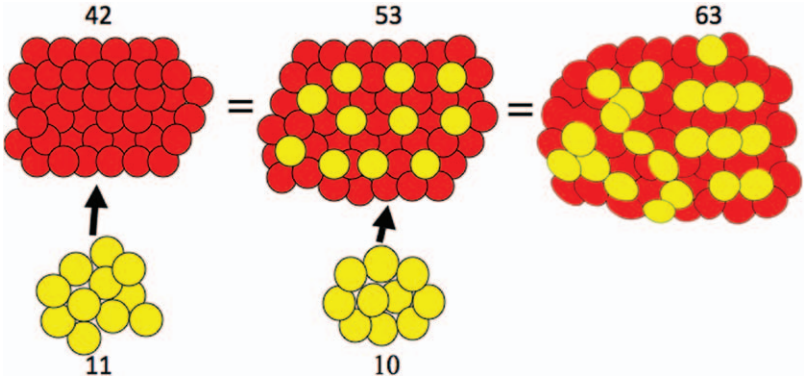

Fig. 1. Theoretical conceptual approximation of the overgrafting theory. Eleven 4-mm yellow droplets can be evenly spread inside a 42-droplet recipient bed without crowding, coalescence, or increased tightness of the recipient. However, squeezing another 10 droplets results in two problems: (1) confluence as droplets coalesce to become larger than 4 mm and end up with central necrosis; and (2) an inability of the recipient bed to expand enough to accommodate the additional size increase, after which the interstitial pressure will rise to choke the circulation and cause additional necrosis.

interstitial fluid pressure, a tightly guarded physiologic value,[29] suddenly increases.[30] As interstitial fluid pressure rises, capillary circulation drops precipitously,[31–34] inhibiting oxygen delivery, neovascularization, and subsequent graft survival. Therefore, even if the utmost care is taken in dispersing the microfat droplets and ribbons, we conclude that too much fat stuffed into too little space with limited compliance creates a choke effect and some, if not all, of the fat cells will not survive (Fig. 1).

The limit to how much we can graft, even with extreme care, is the interstitial fluid pressure of the recipient site as it accommodates the added graft volume. With small volume increases, the tissues are relatively compliant; however, as the volume grafted into a small recipient increases, the compliance drops rapidly, increasing interstitial fluid pressure, decreasing blood flow and oxygen delivery, and ultimately leading to graft necrosis and volume loss (Fig. 2).

Tissues have different volume-to-pressure compliance curves, with subcutaneous tissue being the most compliant; muscle being intermediate; and scarred, irradiated tissue being the worst. Brava preexpansion improves the tissue compliance curve.

Alternate Theory

There is rising interest in a second description as to the fate of grafted adipose tissue. This theory proposes that many of the adipocytes die rather soon, but incumbent stem cells survive and transform their identity to match that of the recipient bed scaffold, in this case, the adipocyte.[25] Multiple investigators are pursuing a goal of enriching fat grafts with stem cells to sidestep the current restrictions.[35] These investigations may eventually lead to new surgical methods that use recent scientific discoveries to improve long-term graft retention. However, none of the methods involving stem cell–enriched grafts have been clinically proven to be more effective and safe. Until then,

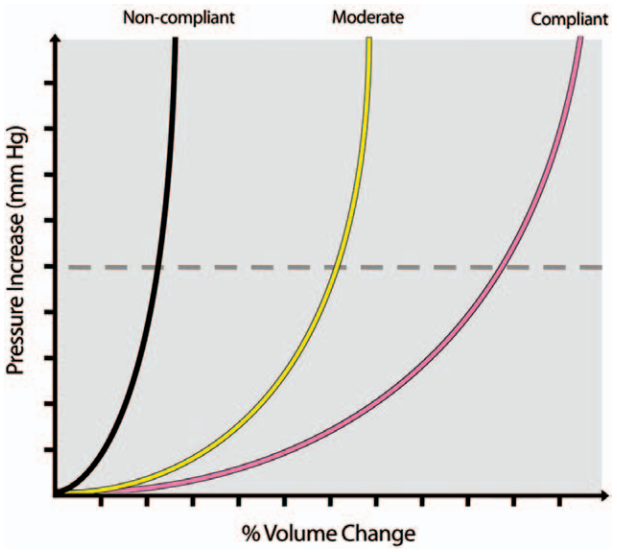

Fig. 2. Theoretical tissue compliance curves. More compliant tissues can accept more graft before the prohibitive interstitial pressure limit is reached (*dashed horizontal line*); beyond a certain point, however, the curve becomes steep and even a minimal amount of additional grafting causes the pressure to increase dramatically.

adhering to the two well-established principles elucidated above is the safest bet.

RECIPIENT-SITE CONSTRAINTS

Small volumes of fat have been grafted successfully into the well-vascularized face,[20] and large volumes have been grafted into the large and well-vascularized muscular buttock.[36] This review is of a different topic: the successful grafting of a large volume into a compact, tight space around the breast or the chest wall after a mastectomy, or worse, after the formation of a highly scarred area from infection, previous operations, irradiation, or a combination of these factors.

Percentage Volume Change

It is all about percentage volume change. Physiologists have measured the interstitial fluid pressure increase per percentage volume change. Subcutaneous tissue is where edema accumulates, where the body sequesters excess fluid, and where tissues are most compliant.[37] Studies have shown that a fluid injection that increases the recipient site by 40 percent causes the interstitial fluid pressure to rise by approximately 10 mmHg. This is within the accepted physiologic range of interstitial fluid pressure variability.[29] However, doubling the recipient-site volume by injecting an additional 60 percent increases the interstitial fluid pressure by approximately 30 mmHg,[30] to reach the danger zone of compartment syndrome and circulatory collapse.[38]

As we move into megavolume grafting, it is the recipient-site percentage volume change that becomes the most crucial factor. A 200-ml volume of fat grafted into a large 2000-ml buttock recipient represents only a 10 percent volume increase and is within the range a buttock can accommodate without a significant interstitial fluid pressure increase. If placed meticulously, most of that graft could theoretically survive. However, trying to graft the same 200 ml of fat into a scarred, irradiated, noncompliant 200-ml mastectomy defect represents a 100 percent volume increase that will drive the interstitial fluid pressure deep into the choke zone. Even with the most meticulous grafting and the very best graft material, this might end up with total graft failure and also may cause necrosis of the recipient tissue and ulceration from the increased interstitial fluid pressure that impedes perfusion.

$$\%\text{Volume change}\,(\Delta) = (\text{Graft volume} + \text{Recipient volume}) / \text{Recipient volume} \quad (1)$$

$$\text{Graft volume} = (\Delta \times \text{Recipient volume}) - \text{Recipient volume}. \quad (2)$$

In contrast, interstitial fluid pressure increase is directly related to percentage volume change (Δ) and inversely related to compliance (f):

$$\text{Interstitial fluid pressure} = \Delta / f \quad (3)$$

$$\Delta = f \times \text{Interstitial fluid pressure}.$$

By substituting in (f × Interstitial fluid pressure) for Δ in equation 2:

$$\text{Graft volume} = (\text{Interstitial fluid pressure} \times f \times \text{Recipient volume}) - \text{Recipient volume}. \quad (4)$$

If interstitial fluid pressure has an upper limit not to be crossed, maximal tolerated graft volume is determined by the compliance of the recipient and its volume. The more compliant and the larger the recipient, the more fat can be grafted (Fig. 3). A crucial principle in megavolume fat graft is to never graft beyond what the recipient site can accommodate.

The Fallacy of Percentage Graft Survival

From the above analysis, we conclude that "percentage graft survival," the commonly used yardstick of graft success, is a misleading concept. It depends on the ratio of graft amount to the welcoming space of the recipient container. A meticulous, careful surgeon, who understands

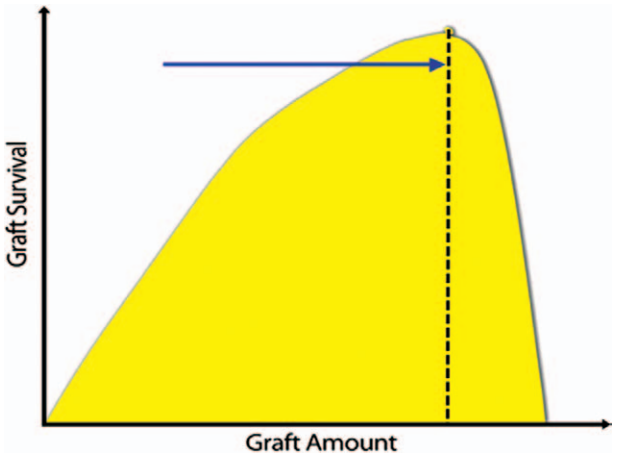

Fig. 3. The proposed last drop effect. There is dramatic loss of fat graft survival when the "one last drop" is injected and causes the interstitial pressure to exceed its maximally tolerable levels, resulting in graft survival "falling off the cliff" (*dashed vertical line*). The larger and more compliant the recipient site, the farther to the right this vertical limit shifts.

the 2-mm limit per graft, and who knows exactly how much the patient's recipient site can tolerate, and who will stop grafting when the interstitial fluid pressure rises to the upper limit of physiologic tolerance, can have close to 100 percent graft survival. However, if in his or her zeal to get the best result he or she pushes beyond that limit, percentage graft survival will rapidly drop and can even approach zero. Unfortunately, in most clinical situations, it is where we want to graft the most that the tissue can accept the least.

This leads to our dictum that the surgeon should never overgraft, that is, to inject more fat than the recipient site can support. If overgrafted, the site may appear satisfactory but the cells are strangled and insufficiently nourished. In this instance, the surgeon took the process over the cliff and subsequently and erroneously concludes that large-volume fat grafting is "unreliable."

The total amount of fat that can be delivered to a recipient area is dependent on the underlying physiologic status of that site. If it is tight and compact, significantly less fat can be grafted, but if the tissues (not the skin) are loose and compliant, more graft can be planted. A strong, significant, positive correlation between Brava preexpansion and resultant augmentation has been described previously.[13] A parabolic curve phenomenon (the cliff) is extant at this point in that one more drop beyond the tissue's capacity to accept can cause a massive loss of graft that provokes the fallacy of "percentage survival" in that it greatly depends on the graft/recipient relationship (Fig. 4). Large-volume increases lead to pathologic interstitial fluid pressure[10] that will not only lead to low graft survival but also induce tissue necrosis. However, low-volume increases will not significantly alter interstitial fluid pressure. In summary, it is allowable to overcorrect but not to overgraft.

A simplified concept of this is the relationship between two-dimensional grafting (skin) and three-dimensional grafting (fat). One cannot graft more skin than the size of the wound defect; similarly, we cannot graft more fat than what the recipient container can accommodate. Overgrafting by staking skin on top of a skin graft will not help survival; similarly, in three-dimensional grafting, crowding more graft material together inside the recipient will choke the entire region and lead to total graft failure

Graft Volume Determination: The Palm Measure

It is naive and presumptuous to harvest fat based on how much we would like to graft. Rather,

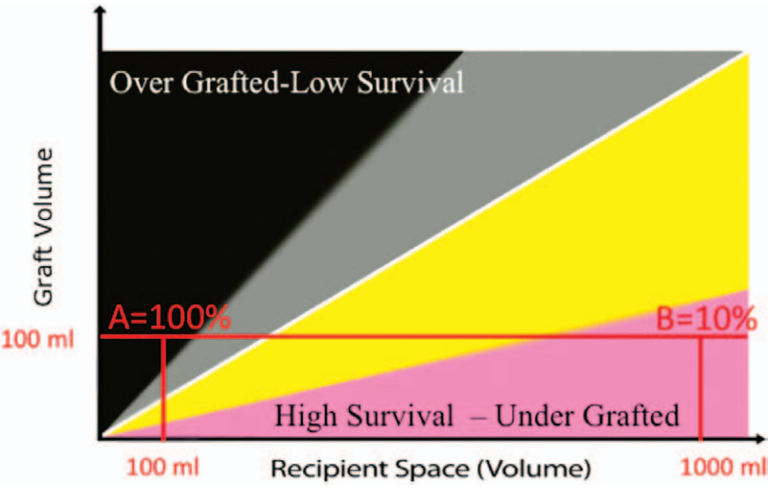

Fig. 4. The fallacy of percentage graft survival. Everything else being equal, a small graft volume placed in a large recipient will have more percentage survival than a large graft volume placed in a small recipient. In *scenario A*, grafting 100 ml into a 100-ml recipient represents a 100 percent graft-to-volume ratio. This doubling of the volume will invariably lead to prohibitive interstitial pressure and necrosis. However, when the same surgeon uses the same technique to graft 100 ml in a larger 1000-ml recipient site of the same patient, there is only a 10 percent volume increase. *Scenario B* is likely to yield excellent survival if the graft is distributed meticulously as microdroplets that do not coalesce. The boundaries of these graft survival zones are not derived from specific experimental data.

it is the graft volume that can be accommodated by the recipient site that determines the amount of fat we harvest at the beginning of the operation. For a rough estimate of the recipient volume, we use the "palm measure" supplemented by an estimate of the thickness of the recipient.

With the palm measure (an average male surgeon's hand is 20 cm from the tips of the fingers to the wrist and 10 cm across), we use a flat palm over the recipient to estimate its surface area as a fraction or a multiple of a 200-cm^2 palm. The recruit-and-pinch technique will give an estimate of tissue thickness and compliance.

Let us consider the case of a medium-framed woman with an A-cup breast size. Her recipient surface area is approximately 250 cm^2 per breast, and we estimate the average thickness of her A-cup breast to be 2 cm and her recipient volume to be 500 ml. If, being young and nulliparous, her firm breasts have relatively low compliance and will not tolerate more than a 20 percent increase in volume, we can graft only 100 ml per breast before interstitial fluid pressure rises to choking levels. Trying to inject more, though easy and tempting, might lead to total graft loss (i.e., falling off the cliff). However, even with the most meticulous and careful placement of the graft microribbons, an 80 percent graft survival will give her an augmentation of 80 ml. However, preexpansion would create a highly compliant recipient tissue bed of 1500 ml (our target goal of three times the original breast volume),[13] allowing us to diffusely inject 300 ml, which is only 20 percent of the new recipient volume. In this situation, an 80 percent graft survival will give her an augmentation of 240 ml (Fig. 5), which is typical of our clinical experience.[13]

Recipient-Site Preparation

From the above, we have concluded that to successfully graft a megavolume of fat (in the 300-ml range for a woman with an A-cup breast), we need compliant tissue that can be expanded to create a megavolume and an abundant blood supply or, at the very least, a highly compliant tissue bed that can accept large graft volumes without significantly increasing interstitial fluid pressure. This challenge is met with the use of the Brava external breast expander, which enables us to increase the tissue compliance, increase the potential recipient space and, equally important, create an abundant stromal/vascular scaffold. Our clinical experience shows that autologous fat transfer breast augmentation is linearly related

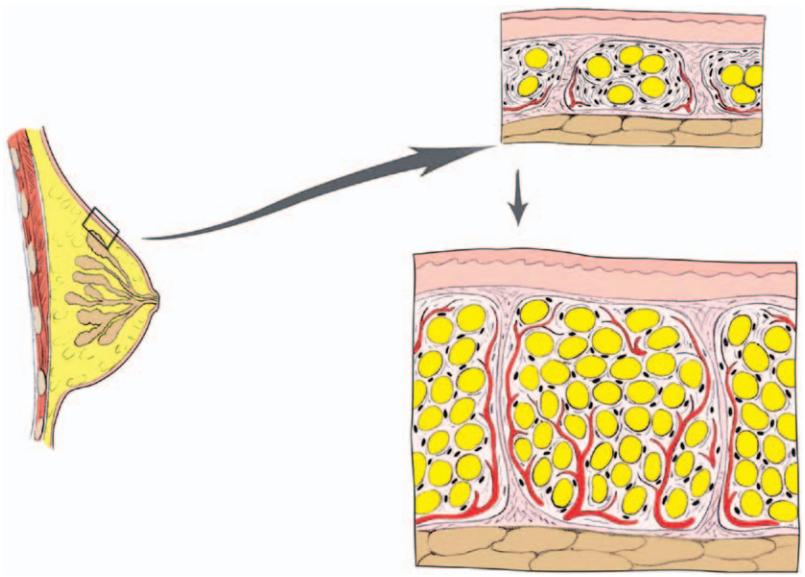

Fig. 5. Expanded tissue can accept more graft. The subcutaneous preglandular tissue is the preferred graft recipient site for breast augmentation. This layer is approximately 1 to 2 cm thick and has limited room for fat grafts. Preexpansion with Brava can potentially increase the thickness of this layer to 3 to 4 cm (Khouri RK, Eisenmann-Klein M, Cardoso E, et al. Brava and autologous fat transfer is a safe and effective breast augmentation alternative: Results of a 6-year, 81-patient, prospective multicenter study. *Plast Reconstr Surg*. 2012;129:1173–1187), allowing it to accept a much larger amount of graft.

to the extent of preoperative expansion with a strong correlation (Pearson correlation coefficient, 0.85) and a 0.7 slope.[13] This confirms that a vital rate-limiting factor in autologous fat transfer breast augmentation is the recipient site. The more she invests in Brava wear, the better she expands, and the larger her resultant breast augmentation. The patient becomes responsible for her final result, and autologous fat transfer breast augmentation becomes a predictable procedure.

However, based on reports of thousands of cases of Brava use, it was understood that, although a painless experience, use of the Brava device was still something for which the patient needed to dedicate herself. Our goal was to expand the breast well beyond the expected enlargement and to keep the device in use until the hour of surgery, and if sufficient expansion was not achieved, the grafting procedure would be postponed (i.e., "no Brava, no breast"). To our knowledge, there is no report of successful single-stage autologous fat graft breast augmentation in the 250-ml range without Brava preexpansion in women with A-cup size breasts.

The major variables determining fat graft retention are graft-to-recipient interface, recipient-site vascularity, and interstitial fluid pressure. External expansion can be used to increase the recipient-site volume and vascularity. This allows microribbons of fat to be distributed diffusely into the breast without causing coalescence or significantly increasing interstitial fluid pressure.

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Plastic Surgery Level of Evidence Rating Scale—Prognostic/Risk Studies

Level of Evidence	Qualifying Studies
I	Highest-quality, multicentered or single-centered, prospective cohort or comparative study with adequate power; or a systematic review of these studies
II	High-quality prospective cohort or comparative study; retrospective cohort or comparative study; untreated controls from a randomized controlled trial; or a systematic review of these studies
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