Vessel diameter discrepancy in end-to-end microvascular anastomosis. A systematic review

Dimitrios Kanakopoulos M.D, MSc^{1,2} Stefanos Tsallas M.D, MSc¹ Evgenios Evgeniou M.D, MSc, FRCS (Plast)² Athanasios Karonidis M.D, PhD¹ Dimosthenis Tsoutsos M.D, PhD¹ Athens, Greece.¹ East Grinstead, UK.²

ORIGINAL ARTICLE

PLASTIC SURGERY

ABSTRACT: Introduction: End-to-end microvascular anastomosis of blood vessels with diameter discrepancy remains a challenging exercise for microsurgeons. Various techniques have been described, but the evidence of consensus directing choice of technique appears lacking. The lack of a standard procedure and categorisation presents a conundrum in the microsurgical community that has resulted in different parties utilising different techniques as per their anecdotal or referred experience. A systematic review of current literature on the topic would provide the best available research evidence.

Methods: Using key words related to the topic, a systematic literature review was conducted in adherence to the principles of PRISMA (2009) statement on MEDLINE, EMBASE, Google Scholar, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials. Search was conducted on studies published in the English language as well as all other languages, from the beginning of time to April 2019, and aimed to search for evidence that directed choice of technique where a discrepancy exists based on patency rates and flap survival. All articles included in the systematic review were critically appraised with the use of appropriate CASP (2018) checklists.

Results: From the literature search 343 potential articles were identified. Of these, nine met both levels of screening for the final critical analysis. No randomised controlled trials or systematic reviews were found. No prospective case series were identified. Data analysis identified evidence of lower overall patency rate at the anastomosis with increasing diameter discrepancy, sloping anastomosis and turbulent blood flow, and succeeded to identify evidence of an effect of technique on patency rate.

Conclusion: The challenge of accomplishing perfect alignment between vessels with different diameter remains arduous. Evidence is available that support the notion, that anastomotic patency increases when turbulent blood flow is eliminated, by using techniques that fashion a slicker conversion and a straight alignment of vessels, hence, promote laminar blood flow. These include the distal tapering technique with sutures or clips and the V-plasty technique.

KEYWORDS: microsurgery, vessel discrepancy, microvascular anastomosis.

Introduction

econstructive microsurgery is a broad and complex surgical field which involves performing free tissue transfer procedures and re-attachment of amputated organs, by anastomosing vessels with a small diameter, using a microscope under high magnification, highly precise purposemade instruments and very fine stitches. The capacity to reinstate continuity and to maintain flow to these miniscule structures has favourably influenced the outcome of treatment of individuals compromised by trauma, cancer or congenital conditions. Nevertheless, despite the evolution in microsurgical techniques, endto-end microvascular anastomosis of blood vessels with diameter discrepancy remains a challenging exercise to microsurgeons. This difference in size uniformity has been observed to lead to significant problems post-surgery.1 Vessel size discrepancy is regarded as significant when it gets to a ratio 4:1 or greater.² Various techniques have been described to problem, including end-to-side overcome this anastomosis which contemplates a sensible option in

significant vessel diameter mismatch, but the evidence of consensus directing choice of technique in end-toend microvascular anastomosis appears lacking.

The lack of a standard procedure categorization presents a conundrum microsurgical community that has resulted in different parties utilising different techniques as per their anecdotal or referred experience. With the need for evidence-based practice increasing over every aspect of medical science, a systematic review of current literature on the topic would provide the best available research evidence. The aim of this exercise is to review techniques used internationally in the management of end-to-end microanastomosis of vessels with diameter discrepancy, to summarise the literature around the topic and to clarify the relative strengths and weaknesses of the literature. The objective is to provide insight to novice as well as experienced microsurgeons, in terms of technique(s) of choice, based on patency rates and free flap survival in patients requiring reconstructive microsurgery with free tissue transfer. We anticipate this will add

From the Plastic & Reconstructive Surgery, Burns and Microsurgery Unit at Hospital "G. Gennimatas". Athens, Greece. And the Plastic & Reconstructive Surgery, Burns and Microsurgery Unit at Queen Victoria Hospital NHS Foundation Trust. East Grinstead, United Kingdom. Received for publication: July 26, 2020. Accepted: July 28,2020.

Systematic Review Flow Chart

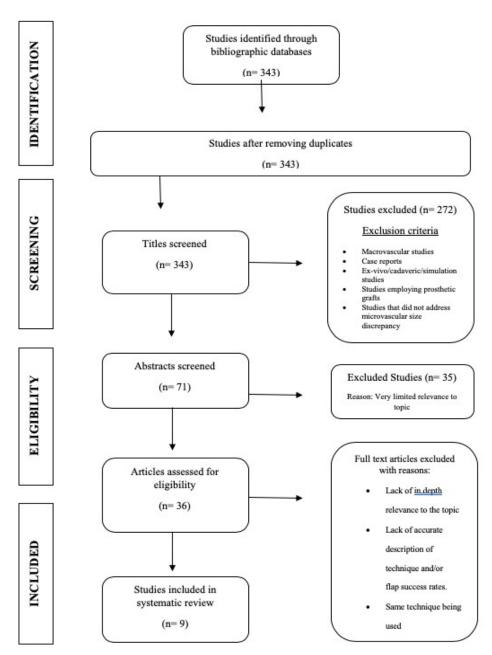


Figure 1. Systematic review flow chart.

substantially to the available evidence for clinical decision-making, in view to allow microsurgeons autonomy in decoding the best evidence.

Methods

The PRISMA framework has been used as a means of designing the outline of this paper. This allowed for an easier sorting process when handling the extensive amounts of literature that returned from inquiry sent to electronic databases.³ The secondary protocol that was followed was the CASP 2018 appraisal method. This tool allowed for each paper to be systematically reviewed by two independent

reviewers and provided an insight into the data which the scholarly articles were pressing. Aside from this, the tool allowed for the assessment of individual articles which were chosen in terms of the strengths and weaknesses that they each might possessed. PRISMA has been used for sorting and layout tasks, while CASP has been used for critical analysis.⁴

The keywords that we used were a combination of 'microsurgery' OR 'microanastomosis' OR 'anastomosis' OR 'microvascular surgery' OR 'vessel size' OR 'vessel diameter' OR 'size' OR 'diameter' AND 'mismatch' OR 'discrepancy'. Search was conducted in studies published in all languages and aimed to search for evidence that directed choice

of technique where a vessel diameter discrepancy exists based on patency rates. Using keywords related to the topic, a systematic literature review was conducted in adherence to the principles of PRISMA 2009 statement on MEDLINE, EMBASE, Google Scholar, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials. These databases are some of the most highly regarded sources of information that could be accessed for the investigative endeavours of this paper (Figure 1). Some databases have been skipped due to lack of resources present to avail their services.

Results

From the literature search 343 potential articles were identified. No randomised controlled trials or systematic reviews were found. No prospective case series were identified. There was a specific focus on the type of operation being related only to microvascular anastomosis. There was a significant degree of corroboration between the articles, which was a result of overlapping areas of investigation between them.⁷

Inclusion criteria encompassed microvascular studies, employing various well-described techniques to anastomose vessels with diameter discrepancy. Exclusion criteria encompassed macrovascular studies, case reports, ex vivo/cadaveric/simulation studies, studies employing prosthetic grafts and studies that did not address microvascular size discrepancy. Of these 343 articles, 272 were excluded based on the abovementioned criteria by screening the title and abstract only, while another 36 articles were excluded due to limited relevance to the topic, i.e. not describing adequately the technique, by screening the entire content of the paper. Only 9 articles met both levels of screening for the final critical analysis, that was in depth relevance to the topic and accurate description of the technique with flap success rates (**Table 1**).8

Important to note is that techniques presented in this paper are interconnected, in that some approaches may be actually modifications or improvements on other base techniques. Through our systematic literature review and analysis of results, it becomes apparent that suturing vessels of unequal diameter in microsurgery is one issue, while avoiding the harmful effects of turbulent blood flow across the anastomosis site is another issue. In our opinion it is not technically sufficient to match the mismatched vessels with any method, if the operator hasn't ensured alleviation of harmful effects of turbulent flow and obtained an optimal blood flow environment across the microanastomosis, that is laminar blood flow. Every novice or experienced microsurgeon coming

across the challenging task to anastomose vessels of diameter discrepancy is recommended to take seriously under consideration the haemodynamic properties of blood flow and to avoid turbulence at the microvascular anastomosis site, which significantly increases the risk of thrombosis and flap failure. 9-11

There is evidence to suggest that blood vessels fashioned to gradually equalize the diameter of the two mismatched vessels, hence gradually reducing the speed of blood flow, pressure and turbulence across the microanastomosis site, as in tapered techniques leading to straight line anastomoses, significantly reduce the risk of thrombosis and flap failure. 12-14

From the available evidence worldwide, our research endeavour reveals that some techniques are superior to other, based on the ability to create a tapered, linear axis structure with laminar blood flow across the microvascular anastomosis, as opposed to other techniques which create abrupt diameter change, or angulation, or furrowing and turbulent blood flow. These techniques are the distal tapering technique and its comparable technique using ligation clips, ¹⁶ and the more recent V-plasty.²

Discussion

There is a variety of techniques used worldwide to address vessel diameter discrepancy in microvascular anastomosis. This paper attempts to offer new insight into a topic by exploring the various aspects which have generally been left largely untouched by the scholar community pertaining to this subject. Undertaking this research effort, we propose the possibility of offering a better overview and comparison of the different techniques that are commonly employed, by conducting a systematic review of each other, in order to better understand their characteristics compared to each other. This assisted in the identification of the best suitable technique(s) for different applications based on the requirements of the microsurgeon.¹⁷

López-Monjardin & De La Peña-Salcedo¹⁸ cite that size discrepancy in anastomosis is a frequently occurring issue in free tissue transfer operations. They demonstrate that the change in the blood vessel size can cause disruptions in the flow of blood and lead to platelet aggregation, which has the potential to cause thrombosis. While the discrepancies have been dealt with through the use of geometrical methods and devices which are low tech, such as jeweller's forceps as well as higher end tech like lasers, the paper concludes that there is no set ideal method which can uniformly handle the vessel size discrepancies on a universal scale. The paper concludes that the best methods of dealing with different discrepancies will be

Reported Success Main findings of study rate	r 98% Spatulated vessel technique (Modified Kunlin's) reliable for usage in end-to-end anastomosis.	1 98.6% A longitudinal incision is made to the smaller vessel equal to its diameter, followed by another similar incision 180 degrees opposite. (Ren anastomosis)	r 100% Fashions both vessels to create a linear axis anastomosis with laminar blood flow	98.6% "Open Y" technique is an alternative option and may be useful when donor vessels with size discrepancies are encountered. Authors propose it in microvascular head and neck reconstruction	100% Branched inter-positional vein grafting and funnel grafting are viable methods for conducting anastomosis	d 100% The usage of ligation clips may be used to decrease the amount of turbulence at the site of end to end anastomosis	%96	100% Sleeve anastomosis techniques presents several advantages	100% Distal tapering provides several advantages over traditional fish mouth anastomosis technique
Discrepancy ratio	1-3:1 or greater	0.8 – 2.5:1	1 – 4:1 or greater	2:1	2 – 5.5:1	Not stated	1.5 – 2:1	2 – 4:1	2 – 2.5:1
Vessel	A - V	A - V	A - V	A only	A - V	V only	A - V	A - V	A only
No. of cases	146	70	41	72	м	10	190	28	7
Level of evidence Oxford (UK) CEBM	LoE 4	LoE 3b	LoE 4	LoE 3b	LoE 4	LoE 4	LoE 4	LoE 4	LoE 4
Study design	Retrospecive case series	Retrospective multicentre case-control study	Retrospective case series	Retrospective individual case-control study	Retrospective case series	Retrospective case series	Retrospective case series	Retrospective case series	Retrospective case series
Journal/ Year	J of Rec Micro 2019	J of Oral Max Surg 2016	J of Rec Micro 2016	Microsurgery 2015	Hand Surgery 2012	J of Rec Micro 2009	J of Rec Micro 2005	Microsurgery 2000	J of Rec Micro 1994
Origin	USA	China	Lebanon	Taiwan	USA	India	Italy	Mexico	Japan
Author	Inbal A et. al.	Ren ZH et al.	Bakhach et al.	Chen et al.	Turker et al.	Suri et al.	De Lorenzi et al.	López Monjardin	Ueda et al.
Research article title	Modified Kunlin's technique for Microsurgical End- to-End Anastomosis	Clinical application of an original vascular anastomosis: A clinical multicenter study	The V-Plasty: A novel microsurgical technique for anastomosis of vessels with marked size discrepancy	Utility of "Open Y" anastomosis technique in the use of superior thyroid artery as recipient vessel for head and neck reconstruction with free flan	Size discrepancy in vessels during microvascular anastomosis: Two techniques to overcome this problem	Managing venous discrepancy: Simple method	Interrupted micromattress sutures solve vessel-size discrepancy	Sleeve anastomosis in head and neck reconstruction	Microarterial anastomosis with a distal tapering
Study No.		7	ю	4	٧.	9	7	∞	6

Table 1. Studies characteristics

on a case by case basis and methods or devices should be selected on specific characteristics as per the requirement.

Tucker and colleagues¹⁹ cite that the anastomotic site is a vital part in the success of operation in microvascular procedures. It is demonstrated that it is imperative that the amount of turbulence in blood flow is kept to a minimum level so that a steady stream of blood flow between the two vessels is maintained.

Harii and Ohmori²⁰ described the oblique incision technique which involves a diagonal cut on the smaller vessel to increase its diameter. Then, a simple end-to-end microvascular anastomosis is performed, yet, with a creation of an angulation at the anastomotic site, a condition which predisposes to turbulence, endothelial damage, platelet aggregation and potential thrombosis. The greater the discrepancy between the two vessels, the greater the oblique cut required to match the vessels, and therefore, the greater the angulation at the anastomosis.² Angulation at the anastomosis has a potential detrimental effect on the patency rate of any microsurgical procedure, with an equivalent risk of flap loss.

Rickard et al.¹² using a computational model, studied and compared experimentally, four different techniques of microvascular anastomosis of vessels with 2:1 diameter mismatch, including the oblique cut and the fish-mouth incision of the smaller vessel, the wedge excision of the larger vessel technique (distal tapering) and the invagination technique. demonstrated that the distal tapering technique blood flow across sustained a laminar microanastomosis, while the other three techniques created turbulence and ring vortex, to suggest that the gentler the slope in the anastomotic site, the more laminar the blood flow, and therefore the highest the patency rates.

It is well recognised that end-to-end eliminates anastomosis or greatly complications which are more commonly associated with end-to-side anastomosis. That is because end-toside anastomosis consists of two vessels connected in a perpendicular fashion, causing sudden shift in the blood flow direction, hence, a significant change in the pressure of blood, which by definition would result in possible blood flow turbulence, endothelial damage, increased platelet aggregation and potential thrombosis. Angulation at the anastomosis has a potential detrimental effect on the patency rate of any microsurgical procedure, with an equivalent risk of flap loss. The abrupt change in the flow dynamics of blood as it crosses the angled microanastomosis causes turbulence which harms the endothelium and sets the ground for potential thrombosis and flap failure.² Connecting the vessels in an end-to-end fashion allows

the flow of the blood to take place without much hindrance.²¹ As the flow of the blood remains the same, there is a decreased chance of pressure difference (Δp) occurring except when there is a more significant discrepancy in size. The larger the discrepancy between the vessels, the more abrupt the change of blood flow at the anastomosis site, the more likely to encounter complications associated with turbulent blood flow, endothelial damage and platelet aggregation with resultant thrombosis and flap failure. Henceforward, the gentler the slope created in mismatched vessels in end-to-end microvascular anastomosis by individual techniques, the least the chance of complications associated with thrombosis and the better the outcomes.

Distal tapering techniques with sutures¹⁵ or with ligation clip(s), 16 perhaps represent two of the most significant methods which take into account the difference in pressure created from the sudden change in the vessel diameter and its effects and represent a procedure to resolve the issues surrounding microsurgical anastomosis of vessels with diameter discrepancy. Tapering technique with sutures creates a wedge cut on the vessel and then sutures it progressively smaller, starting from the larger vessel towards the end of it and to the smaller vessel, while the similar technique with ligation clips tapers the larger vessel in an oblique manner towards the opposite end using ligation clip(s). This tapering causes the Δp between the two vessels to balance out over time. Instead of being subjected to a sudden change in Δp , the blood now experiences a lower force overtime of Δp , which preserves the integrity of the vessel structure as well as the microvascular anastomosis site.²² The tapered gradient of the vessel provides the blood with a less of a change in the amount of pressure over a longer period of time as contrasted with the sudden shift that would occur if the there was no tapering present. From the literature review, these techniques may be applied universally in end-to-end microsurgical anastomosis of vessels with diameter discrepancy. Yet, these two techniques don't come without limitations. The suturing tapering technique requires more than usual suturing material, which in turn has a potential thrombogenic effect as well as require more time to be placed. On the other hand, the ligation clip is a foreign body, and thus has the chance to migrate from the application site, with detrimental consequences. In addition, the tapering step will require some vascular material which can be tapered. This can present a potential problem in cases where there may be extensively damaged or atherosclerotic vessels, or where there may not be enough spare vessel available for the tapering procedures to the carried out. Furthermore, tapering can require a certain amount of skill from the

microsurgeon, as they will have to take into account the gradient at which the tapering is occurring. Too steep or flat of a taper will not be effective in mitigating the effects of Δp .²³

The other technique that promotes laminar flow through a straight-line microvascular anastomosis is the V-plasty, which fashions both vessels ends to match the discrepancy. In the larger vessel, V-shaped flap is created, the size of which is dependent on the size of the smaller vessel. On the smaller vessel, an incision is made to fashion a triangular defect, the depth of which should match the dimension of the Vshaped flap of the larger vessel. It is safely applicable in all discrepancy ratios and the authors illustrate a detailed mathematical calculation of the dimensions of the V-plasty depending on different sizes of vessels, which maintains a linear axis and laminar blood flow through the anastomosis for respective discrepancy ratios. This technique's weakness is the lack of simplicity in its design, and the expert microsurgical skill required to execute it.

different ofThe number methods demonstrated within the studies is corroborative evidence of the fact that no standard universal technique exists worldwide to resolve this issue. Different cases of anastomosis may require a case by case analysis on what method is to be used, as there is a general lack of consensus between microsurgeons in terms of the technique of choice. This great diversity demonstrates that there are different standards regarding this over the entire world and that they are practised based on the parameters of those who are operating under those respected regions or locales. This may be as a result of the limited amount of literature that is available on the topic, which represents an important factor that appoints great significance to the issue. There is also a lack of systematic review of various techniques used across the globe. This is a problematic aspect, because of the factor that different surgeons may be using techniques overcome vessel diameter mismatch microvascular anastomosis, with a degree of critical inaccuracy and appraisal compared to techniques. This means there is no generally established and accepted standard which has been created to streamline and optimise the overall process.

Conclussion

Patent vascular anastomosis is undoubtedly one of the most significant factors influencing free flap outcome after microsurgical reconstruction. There is, in fact, a lack of a standard in terms of categorising and extensively describing, analysing and presenting information on the different microvascular anastomosis techniques in vessels with diameter

discrepancy. This was observable throughout all the articles which were analysed. They all presented the conundrum of not having a standard reference they could use in their operations and as such often had to rely to what they already knew or being experimental and trying out their own techniques. The lack of homogeneity amongst relevant clinical articles deemed a meta-analysis impossible, as there were no two or more primary studies that addressed the same hypothesis in the same way and there was no randomised control trials comparing techniques. Homogeneity was only found in animalmodel experimental research articles. There was also some bias present within the studies; this was mainly connected to the usage of techniques which the microsurgeons were most familiar with. familiarity led to them consistently using the same technique, led to them becoming significantly biased in their approach on how they evaluated the efficacy of the different microvascular anastomosis techniques. Despite the scarcity of research and the limitations faced, this systematic review demonstrates that there is enough research evidence to suggest microsurgical anastomosis of vessels in an angled or perpendicular position renders the site prone to turbulent blood flow, endothelial damage, platelet aggregation and potential thrombosis, catastrophic results to the reconstruction executed. In a systematic approach, this study examined the international scientific literature to identify which techniques eliminate the element of turbulence and its adverse effects, clearly highlighting the superiority of some techniques over some other, in terms of patency rates.

High level of microsurgical skill is required to perform either technique, therefore constant practice and proficiency in the field is mandatory. Adhering to basic microsurgical principles and respecting blood flow dynamics may be much more important than any technique performed, but there is yet a lot of work to be done to bridge this knowledge deficiency. To bridge the potential gap of knowledge in this challenging field, further research is strongly recommended, ideally in the form of an international, multicentre, randomised control trial with a high study power. There is also a need to investigate the creation of a standard system to present the information in a comprehensive manner to the microsurgical community.

Limitations

The scarce of a considerable amount of well-designed, quality literature, was a limitation of our paper and demonstrates that this area has not been adequately explored. The scarcity of exploration is

corroborated with the lack of consensus amongst the different surgeons who are related to the field of microsurgery.²⁴

Conflicts of interest

The authors declare no conflicts of interests.

References

- Wong CH, Wei FC. Microsurgical free flap in head and neck reconstruction. Head & neck. 2010 Sep;32(9):1236-45
- Bakhach J, Dido S, Zgheib E, Papazian N. The V-plasty: A novel microsurgical technique for anastomosis of vessels with marked size discrepancy. J Reconstr Microsurg 2016;32:128-136
- Moher D, Liberati A, Tetzlaff JA, Altman D. PRISMA 2009 flow diagram. The PRISMA statement. 2009;6:1000097.
- 4. Heyvaert M, Hannes K, Maes B, Onghena P. Critical appraisal of mixed methods studies. Journal of mixed methods research. 2013 Oct;7(4):302-27.
- 5. Healey M, Healey RL. How to conduct a literature search. Key methods in geography. 2010 May 19;2:16-34.
- Henry S, McInnes BT. Literature based discovery: models, methods, and trends. Journal of biomedical informatics. 2017 Oct 1;74:20-32.
- Tricco AC, Lillie E, Zarin W, O'Brien K, Colquhoun H, Kastner M, Levac D, Ng C, Sharpe JP, Wilson K, Kenny M. A scoping review on the conduct and reporting of scoping reviews. BMC medical research methodology. 2016 Dec;16(1):15
- 8. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation science. 2010 Dec;5(1):69.
- Harris JR, Seikaly H, Calhoun K, Daugherty E. Effect of diameter of microvacular interposition vein grafts on vessel patency and free flap survival in the rat model. J Otolaryngol 28;152-157, 1999
- Hayhurst JW, O'Brien BM. An experimental study of microvascular technique, patency rates and related factors. Br J Plast Surg 28;128-132, 1975
- Monsivais JJ. Microvascular grafts: effect of diameter discrepancy on patency rates. Microsurgery 11;285-287, 1990
- 12. Rickard RF, Meyer C, Hudson DA. Computational modelling of microarterial anastomoses with size discrepancy (small-to-large). J Surg Res 2009;153(1):1-11
- Ahn CY, Borud LJ, Shaw WW. Analysis of suturing techniques in the microvascular anastomosis of vessels of unequal diameter. Ann Plast Surg 32;469-473, 1994.
- Boeckx W, De Lorenzi F, van der Hulst R. Increasing the flow output by Y-shaped microvascular anastomosis. J Reconstr Microsurg 18;381-386, 2002
- 15. Ueda K, Harashina T, Inoue T, Kurihara T, Harada T, Oba S. Microarterial anastomosis with a distal tapering technique. Journal of reconstructive microsurgery. 1994 Mar;10(02):87-90.
- Suri MP, Ahmad QG, Yadav PS. Managing venous discrepancy: simple method. Journal of reconstructive microsurgery. 2009 Nov;25(08):497-9.
- 17. Kansy K, Mueller AA, Mücke T, Koersgen F, Wolff KD, Zeilhofer HF, Hölzle F, Pradel W, Schneider M, Kolk A, Smeets R. Microsurgical reconstruction of the head and neck region: Current concepts of maxillofacial surgery units

- worldwide. Journal of Cranio-Maxillofacial Surgery. 2015 Oct 1;43(8):1364-8.
- López-Monjardin H, de la Peña-Salcedo JA. Techniques for management of size discrepancies in microvascular anastomosis. Microsurgery: Official Journal of the International Microsurgical Society and the European Federation of Societies for Microsurgery. 2000;20(4):162-6.
- Turker T, Tsai TM, Thirkannad S. Size discrepancy in vessels during microvascular anastomosis: Two techniques to overcome this problem. Hand Surgery. 2012;17(03):413-7.
- Harii K, Ohmori K. Free skin flap transfer. Clin Plast Surg 1976;3(1):111-127
- Cho EH, Garcia RM, Blau J, Levinson H, Erdmann D, Levin LS, Hollenbeck ST. Microvascular anastomoses using end-to-end versus end-to-side technique in lower extremity free tissue transfer. Journal of reconstructive microsurgery. 2016 Feb;32(02):114-20
- Biemer E, Duspiva W. Reconstructive microvascular surgery. Springer Science & Business Media; 2012 Dec 6.
- 23. Olszewski WL, editor. Handbook of microsurgery. CRC Press; 2019 Jun 13.
- 24. Balasundaram, I., Aggarwal, R. and Darzi, L.A., 2010. Development of a training curriculum for microsurgery. British journal of oral and maxillofacial surgery, 48(8), pp.598-606.

Dimitrios Kanakopoulos M.D.
Plastic & Reconstructive Surgery, Burns and
Microsurgery Unit,
Queen Victoria Hospital NHS Foundation
Trust, East Grinstead, United Kingdom
dr.kanakopoulos@gmail.com