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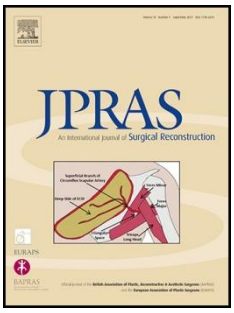

Title: Perforator mapping reduces the operative time of DIEP flap breast reconstruction: a systematic review and meta-analysis of preoperative ultrasound, computed tomography and magnetic resonance angiography

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Title

Perforator Mapping Reduces the Operative Time of DIEP Flap Breast Reconstruction: A Systematic Review and Meta-Analysis of Preoperative Ultrasound, Computed Tomography and Magnetic Resonance Angiography

Running Head

DIEP mapping saves operative time

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Competing Interests

None declared

Key words

Breast reconstruction; DIEP; perforator; mapping; review

Compliance with Ethical Standards

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Conflicts of Interest

There are no conflicts of interest.

Ethical review

Ethical review was not required as this is a review of published literature. Further, this article does not contain any studies with human participants, which were originally performed by any of the authors.

Abstract

Background: Prior to DIEP flap breast reconstruction, mapping the perforators of the lower abdominal wall using ultrasound, computed tomography angiography (CTA) or magnetic resonance angiography (MRA) reduces the risk of flap failure. This review aimed to investigate the additional potential benefit of a reduction in operating time.

Methods: We systematically searched the literature for studies concerning adult women undergoing DIEP flap breast reconstruction, which directly compared the operating times and adverse outcomes for those with and without preoperative perforator mapping by ultrasound, CTA or MRA. Outcomes were extracted, data meta-analysed and the quality of the evidence appraised.

Results: Fourteen articles were included. Preoperative perforator mapping by CTA or MRA significantly reduced operating time (mean reduction of 54 minutes [95% CI 3, 105], p=0.04), when directly compared to DIEP flap breast reconstruction with no perforator mapping. Further, perforator mapping by CTA was superior to ultrasound, as CTA saved more time in theatre (mean reduction of 58 minutes [95% CI 25, 91], p<0.001) and was associated with a lower risk of partial flap failure (RR 0.15 [95% CI 0.04, 0.6], p=0.007). All studies were at risk of methodological bias and the quality of the evidence was very low.

Conclusions: The quality of research regarding perforator mapping prior to DIEP flap breast reconstruction is poor and although preoperative angiography appears save operative time, reduce morbidity and confer cost savings, higher quality research is needed.

Registration: PROSPERO ID CRD42017065012

Introduction

As the incidence of breast cancer continues to rise[1], more women are undergoing mastectomy and breast reconstruction[2]. Autologous tissue breast reconstruction offers the greatest patient satisfaction[3], so its use is gaining popularity worldwide[4] with the deep inferior epigastric perforator (DIEP) flap evolving as the ideal choice for autologous reconstruction in suitable women. Breast reconstruction with DIEP flap(s) is associated with lower risks of adverse outcomes[5], favourable donor site morbidity[6–9], improved quality of life[10], shorter hospital stay[11,12], reduced postoperative pain[13–15] and superior cosmetic results[16], compared to breast reconstruction using other flaps and a substantially lower risk of failure when compared to implants[5,17,18].

To reduce the risk of complications and improve the efficiency of flap harvest, many surgeons use preoperative perforating mapping of the lower abdominal wall. Current options[19] include: duplex ultrasound; computed tomography angiography (CTA) with intravenous iodinated contrast and magnetic resonance angiography (MRA) with intravenous gadolinium. Recent reviews have shown that perforator mapping significantly reduces the risks of total and partial flap failure[20] as well as hospital stay[21]. Axial imaging with CTA/MRA also provides an opportunity to detect 'incidentalomas' or occult recurrence[19], which could substantially change management[22–24]. Further, Offodile and colleagues[25] showed that perforator mapping by CTA was cost-effective given morbidity reductions and improved quality of life when compared to DIEP flap breast reconstruction without preoperative imaging, which is associated with higher risks of complication. However, to-date there is no reliable evidence that perforator mapping reduces operating time. Reducing operating time has the potential to confer considerable cost-savings, reduce morbidity and therefore, improve patient outcomes.

We aimed to investigate the hypothesis that preoperative perforator mapping by ultrasound, CTA or MRA prior to DIEP flap breast reconstruction, reduces operating time.

Methods

This review is registered on the PROSPERO database (CRD42017065012); it was designed and conducted in accordance with the Cochrane Handbook of Systematic Reviews[26] and has been authored in accordance with the PRISMA checklist[27].

Search Strategy

Both Medline and EMBASE were interrogated by two independent authors, using the NICE Healthcare Database (www.hdas.nice.org.uk) and the terms DIE?P.ti,ab OR ((((deep AND inferior) AND epigastric) AND artery) AND perforator).ti,ab AND Breast reconstruction.ti,ab OR mammoplasty.ti,ab AND imag*.ti,ab OR map*.ti,ab OR plan*.ti,ab OR angiogr*.ti,ab OR C?T*.ti,ab OR computed AND tomography.ti,ab OR magnetic AND resonance.ti,ab OR MR*.ti,ab OR ultra?so*.ti,ab OR duplex.ti,ab OR doppler.ti,ab. No language restrictions were applied. This yielded 417 hits in EMBASE and 572 in Medline on 7th August 2017. Searches were de-duplicated and screened according to a customised and previously piloted in/out form, by two independent authors. The full texts of all potentially relevant articles were obtained in accordance with our protocol (available at https://www.crd.york.ac.uk) except for one which was unobtainable[28]. The reference lists for all screened articles were also scrutinised for potentially relevant papers. Final lists of included articles were compared and disagreements resolved by discussion.

Study Selection Criteria

This review considers adult women (over the age of 18 years) undergoing breast reconstruction after mastectomy, using the DIEP flap. We considered articles that directly compared the operating times of DIEP flap breast reconstructions with preoperative perforator mapping (by imaging with CTA, MRA or ultrasound) against those women undergoing surgery without preoperative perforator mapping.

The primary outcome is the difference in operative time, measured in minutes. We considered total operative time, flap harvest time and any other (undefined) operating time reported as analogous because time savings due to the intervention (in a direct comparison study where all other factors

are constant) are likely to be due to reductions in the flap harvesting time. Further, time is a scaled outcome with ratio property, so between-group differences in flap harvest time will be equal to differences in total operative time again supporting the concept that pooling is acceptable. Observational research rarely generates similar baseline groups, so we planned to use adjusted estimates of operating time. Secondary outcomes included total flap failure (defined as failure which required removal of the entire flap) and partial flap failure (defined as failure of a portion of the flap which required debridement but not complete removal), recorded as binary outcomes.

Data extraction

We extracted details of the study design and the statistics for operating time, flap harvest time or any permutation of these alongside the frequency of total flap loss and partial flap loss. Where data was missing or unclear, we contacted the corresponding author by email and/or phone and if no reply was received, then 4 weeks later all authors were contacted in addition to re-contacting the corresponding author.

Nineteen articles were eligible. Two conference abstracts[29,30] were excluded for lack of data. Re-publication of similar data was encountered twice: Masia and colleagues published four articles which appeared to contain similar data; their 2010 article[31] was similar (albeit with a different sample size) to another article[32] and two conference abstracts[33] but all lacked the standard deviations for the mean times reported or p-values for the comparisons, which would have enabled back-calculation, so were excluded. Minqiang et al simultaneously published similar work in the English[34] and Chinese[35] literature in 2010, although the sample size in the latter article is slightly larger (56 vs. 44) and therefore, we have utilised the larger dataset in the meta-analyses and consulted both articles to assess the risk of methodological bias.

Seven included articles omitted the standard deviations of the mean times reported in the published works; one group provided the missing data[36] whilst the other was unable[37] so we include data from their unilateral cases only. Missing standard deviations were imputed using the Cochrane RevMan Calculator.

Assessment of Bias

The risk of methodological bias was assessed by two review authors independently, using the ROBINS-I tool[38]. Similarly, the overall quality of the evidence was independently assessed by two review authors using the GRADE tool[39].

Analysis

We performed direct comparison meta-analyses using Review Manager® version 5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to calculate mean differences in operating time and relative risk ratios (RR) for adverse outcomes with 95% confidence intervals (CI), using the inverse variance and Mantel-Haenszel tests, respectively. Random-effects models were used for except one analysis, due to statistical heterogeneity as quantified by the I^2 statistic. The patient/woman was the unit of analysis and not the flap[40,41]. Significance was set as 5%. There was insufficient data for any meaningful assessment of publication bias.

Results

We included 14 articles[35–37,42–44,21,45–50] (Figure 1), the characteristics of which are summarised in Table 1.

Preoperative perforator mapping by CTA or MRA saved a mean of 54 minutes (95% CI 3 to 105 minutes, Figure 2). However, there was significant statistical heterogeneity, all studies were at high risk of methodological biases and the quality of the evidence is very low (GRADE score +1; downgraded once for methodological concerns).

Subgroup analyses in Figure 3 show that perforator mapping by CTA appears superior to ultrasound, given that CTA reduced operating time by a mean of 58 minutes (95% CI 25 to 91 minutes). Again, there was significant statistical heterogeneity, all studies were at risk of methodological biases and the quality of the evidence is very low (GRADE score 0; downgraded once for methodological concerns and once for consistency). We performed a sensitivity analysis by removing studies at high risk of methodological bias[42,36,44] and CTA remained superior to ultrasound (saving a mean of 72 minutes [95% CI 33, 112], p<0.001).

The risk of total flap loss was not different between women who had perforator mapping by CTA or ultrasound (Figure 4). All studies were at risk of methodological biases and the quality of this evidence is very low (GRADE score +1; downgraded once for methodological concerns).

The risk of partial flap loss was 80% lower when perforator mapping was performed by CTA (RR 0.2 [95% CI 0.04 to 0.6]; Figure 5). A sensitivity analysis performed by removing the study[34] at high risk of methodological bias strengthened this association, such that CTA perforator mapping again appeared to reduce the risk of partial flap loss. The absence of statistical heterogeneity improves the confidence in this estimate and justifies the choice for a fixed-effects model. However, the quality of the evidence is again very low (GRADE score +1; downgraded once for methodological concerns).

For bilateral DIEP flap breast reconstructions, perforator mapping with either CTA or MRA did not significantly alter operative time (mean difference of 34 minutes [95% CI 33, 101], p=0.32 favouring CTA). Similarly, operating time after perforator mapping with CTA was not different to ultrasound (mean difference 80 minutes [95% CI 11, 170], p=0.08 favouring CTA). There was insufficient data to perform meta-analysis of the risks of total or partial flap loss for women undergoing bilateral DIEP flap breast reconstruction. All included studies reporting the outcomes of bilateral reconstruction were at high risk of methodological bias and the quality of the evidence is very low (GRADE score +1; downgraded once for methodological concerns).

Risk of bias

All studies were at risk of methodological biases (Figure 6) and this limits the external validity of our findings. Our reasons for declaring some studies at high risk of bias in certain domains are as follows:

- Five studies were missing standard deviations[48,51,37,45,46] which prevents inference about the spread of data and required imputation for this review, which will bias the results towards no effect and as such, we designated these studies at high risk of bias due to missing data.
- Casey et al[42] tabulated baseline between-group differences but omitted the p-values from the following tests of proportion: operating surgeons A vs. B vs. C, unilateral vs. bilateral reconstructions and; immediate vs. delayed cases. We analysed these proportions and they represent significant baseline imbalances ($p<0.001$, $p=0.005$ and $p=0.0001$, respectively) which could confound the outcome. It is unclear why these comparisons were omitted, so we have graded this study at high risk of 'bias due to confounding' and 'bias in the selection of reported results'.
- Klasson et al[44] was graded as high risk of 'bias in selection of the reported results' given that there was one case lost to follow-up in the CTA group but incomplete data is still reported, and one case in the ultrasound group was excluded as the operation was very long and designated an outlier.
- We judged Minqiang et al to be at high risk of methodological bias in several domains. Three DIEPs were converted to SIEA/TRAM flaps but included in the DIEP group analyses

(which is reflected in the judgement of high risk of 'bias in classicisation of the intervention') and this may bias the outcome in favour of mapping because SIEA and TRAM flaps are typically easier (and so faster) to harvest. The duality of publications[34,35] with differences in the published data which we have designated high risk of bias due to missing data and selective reporting.

- Tong et al[48] was judged to be at high risk of bias of misclassification of the intervention and deviation from the intended intervention because they stated that "*patients who had CTA for the purpose of preoperative planning for free flap reconstruction but did not undergo surgery were included in this study*" which could affect the outcome.
- Significant baseline imbalances were the reason that Vargas et al[50] was judged at high risk of bias due to confounding. Ideally, they would also have adjusted their estimates for baseline differences in a multivariable model.

Discussion

This review highlights the paucity of high quality of research concerning perforator mapping prior to DIEP flap breast reconstruction. We have shown that perforator mapping prior to DIEP flap breast reconstruction by axial imaging (by CTA or MRA) may reduce operating time and the risk of partial flap loss, which is in keeping with the evolving literature, but concerns over the quality of the primary data means that the outcome is not reliable.

Our meta-analyses suggest that preoperative perforator mapping saves approximately one hour in theatre. The importance of reducing operating time should not be underestimated because operating time is independently associated with increased risks of flap failure[52–54], venous thromboembolic events[55] and infection[56]. Therefore, preoperative identification of the dominant perforator supplying the flap may expedite flap harvest and such time savings could in-turn reduce the risks of adverse outcomes. A recent health economic review of CTA prior to DIEP flap breast reconstruction concluded that perforator mapping by CTA was more cost-effective than ultrasound[25]; this was based upon a better quality of life in the CTA group owing to lower risks of flap loss and fat necrosis. Further, they stated that provide CTA reduced operating time by more than 21 minutes then it "*would always be cost-effective*". We have shown a significant and clinically important reduction in operating time which satisfies this condition. Further, if the cost per minute to run an operating theatre for a DIEP flap breast reconstruction were $53 in the USA[57] or £11.3 in the UK, then by mapping we could save $2862 in the USA (95% CI $159, $5565) and £610 in the UK (95% CI £34, £1187), per patient. The per-procedure cost of a mapping CTA is $1562 in the USA and £60 in the UK. Therefore, with approximately 833 women undergoing free flap breast reconstruction per year in the UK (most of whom receive a DIEP flap)[18], the potential cost savings per annum is approximately £0.5million. However, differences in the observed operating time between groups could also be explained by methodological biases or confounding variables, both of which are certainly present in the included studies. For those wishing to setup a perforator mapping service, we provide the scanning protocols for included studies in Appendix 1 (supplementary online material). We invite further prospective research and economic analyses

into the potential improved cost utility[58] of perforator mapping prior to DIEP flap breast reconstruction; ideally, these would be investigated in randomised trials.

The benefits of perforator mapping must be weighed against the potential risks of medical imaging. Safety is of paramount importance and whilst ultrasound may be inferior to CTA/MRA in many ways, ultrasound remains popular because it is universally considered to be safe. Conversely, a typical CTA of the lower abdominal wall delivers 6-10 millisieverts (mSv), which does incur a statistically small but significantly increased risk of developing a de-novo cancer[59,60]. Rozen extrapolated this to infer that approximately 1 in 1050 women would develop an extra cancer attributable to mapping CTA (at 8.18mSv)[61]. Whilst magnetic resonance imaging does not pose any biological risk[62], there are absolute contra-indications (metal in the eyes or brain given the risk of haemorrhage or visual loss respectively, and implants which are not “MR-safe” given the risk of burns or dysfunction), relative contra-indications (such as pregnancy[63] and claustrophobia) and common side effects such as nausea, vertigo and temporary neuro-behavioural changes. Intravenous gadolinium was used in all included articles and provides the chief unpredictable risk for patients; gadolinium shorten the T1, improving fluid signal albeit not a ‘contrast medium’ in the strictest sense. Whilst old formulations of gadolinium conferred a small risk of nephrogenic systemic fibrosis owing to Gd^{3+} deposition, subsequent formulations based on a stronger chelator (DTPA) have all-but eliminated this concern. All current gadolinium based agents pose a dose-dependent risk of adverse reaction with 1 in 100 being affected; most are transient hypersensitivity reactions but there is a 3 in 10,000 risk of death from anaphylaxis, typically affecting women with drug hypersensitivities.[64] Therefore, whilst CTA and MRA may provide more useful information than ultrasound, there are risks which must be considered. To better explore this topic, we recommend a systematic review and meta-analysis of the diagnostic accuracy of CTA versus MRA for the identification of the dominant perforator in unilateral DIEP flap breast reconstruction. Once the best test (CTA or MRA) is defined, then the cost utility can be better investigated and policy recommendations made.

Limitations

Heterogeneity in the outcomes is important to consider because observed differences in the outcome may derive from statistical and/or clinical differences, which in-turn may confound the outcome. Regarding the differences in operative time associated with perforator mapping (Figure 2) - heterogeneity may explain this difference, with baseline between-group differences favouring the mapping group, for example the mapping group may more: slimmer patients in which flap harvest is easier; patients operated on by senior (and so efficient) surgeons; immediate reconstructions which are quicker because the breast pocket and recipient vessel dissections may be less hostile, etc. It is likely there are systematic differences between studies because there are outliers in the meta-analyses (Figures 2 and 3) but the origin is unclear. Alternatively, the observed superiority of mapping may be due to statistical heterogeneity, which is high as represented by the I^2 statistic and other factors, given that the original estimates were not adjusted for potential confounders. All such methodological biases were observed in the included studies, as depicted in the traffic light system alongside each forest plot. Whilst we used a random-effects model to generate conservative estimates and better accommodate the observed heterogeneity, readers should be cautious interpreting our data as we feel that the data is most useful for hypothesis genesis, rather than decision-making. As three articles (Table 1) did not detail the parameters of the CTA it is impossible to replicate their methods and as such, the usefulness of the data is reduced.

Conclusions

We have shown that the quality of evidence regarding perforator mapping for DIEP flap breast reconstruction is poor and as such, our findings have limited external validity. Whilst our review suggests that preoperative perforator mapping in DIEP flap breast reconstruction reduces operating time and morbidity, which is consistent with the evolving literature, we conclude that higher quality data is needed from well-designed and conducted randomised trials.

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Figure Legends

Figure 1. PRISMA flowchart

Figure 2 – Mean Difference in Operating Time. Forest plot showing that preoperative mapping by CTA or MRA significantly reduces operating time of unilateral DIEP flap breast reconstruction, compared to no mapping alongside the risk of methodological bias assessments.

Figure 3 – Mean Difference in Operating Time. Forest plot showing that preoperative CTA is preferable to Ultrasound for reducing the operative time of unilateral DIEP flap breast reconstruction, alongside the risk of methodological bias assessments.

Figure 4 - Risk of Total Flap Failure. Forest plot showing no evidence of a difference in the risk of total flap failure for studies comparing mapping by CTA and ultrasound in unilateral DIEP flap breast reconstruction, alongside the risk of methodological bias assessments.

Figure 5 - Risk of Partial Flap Failure. Forest plot showing that preoperative mapping by CTA significantly reduces the risk of partial flap failure compared to ultrasound in unilateral DIEP flap breast reconstruction, alongside the risk of methodological bias assessments.

Figure 6 - Risk of bias summary. Review authors' judgements about the risk of bias. Green denotes low risk, yellow unclear risk and the red high risk.

Table 1. Study characteristics for women undergoing DIEP flap breast reconstruction. Details of each study's imaging parameters can be found in Appendix 1 (supplementary online material).

			Study Sample				Perforator mapping methods compared	
Study	**Location**	**Participant enrolment**	N	Mean age in years	Immediate : delayed	Unilateral: bilateral	Method #1	Method #2
Casey 2009[42]	USA	Retrospective	213	52	Unknown	139:74	Handheld doppler ultrasound performed and interpreted by unknown operator(s)	CT angiography (64-row detector); image reconstruction and interpretation were not described
Fansa 2011[37]	Germany	Retrospective	21	54	Unknown	21:0	No mapping	CT angiography (64-row detector); image reconstruction and interpretation were not described
Gacto-Sanchez 2010[43]	Spain	Mixed	70	48	0:70	0:70	Handheld doppler ultrasound performed and interpreted by unknown operator(s)	CT angiography (16-row detector); images were reconstructed and interpreted by a radiologist
Ghattuara 2010[51]	UK	Retrospective	100	47	Unknown	74:26	No mapping	CT angiography (32-row detector); images were reconstructed and interpreted by a radiologist
Klasson 2015[44]	Sweden	Quasi-Randomised Trial	63	54	Unknown	Unknown	Handheld doppler ultrasound performed and interpreted by the operating surgeon using an 8MHz probe	CT angiography (16- or 42-row detector); images were reconstructed and interpreted by one radiologist
Malhotra 2013[21]	UK	Retrospective	200	49	1:1	Unknown	Phillips iU22 xMATRIX (8-15MHz) ultrasound performed by an unknown operator. Images reported by one radiologist	CT angiography (64-row detector); images were reconstructed and interpreted by one radiologist
Minqiang 2010[35]	China	Mixed	56	Unknown	Unknown	Unknown	Doppler sonography performed and interpreted by unknown operator(s)	CT angiography (64-row detector); image reconstruction and interpretation were not described
O'Connor 2016[36]	UK	Retrospective	540	Unknown	229:246	36:29	Handheld doppler ultrasound performed and interpreted by unknown operator(s)	CTA methodology not described
Rozen 2008[45]	Australia	Mixed	88	Unknown	Unknown	9:2	Doppler ultrasound performed and interpreted by unknown operator(s)	CT angiography (64-row detector); images were reconstructed but how they were interpreted is not described
Schaverien 2011[46]	UK	Retrospective	119	49	53:66	6:1	No mapping	MRI angiography (1.5 Tesla) ; image reconstruction and interpretation were not described
Smit 2009[47]	Sweden	Retrospective	138	50	~5:8	~5:1	Doppler ultrasound performed and interpreted by unknown operator(s)	CT angiography (16-row detector); image reconstruction and interpretation were not described

Tong 2012[48]	USA	Retrospective	69	49	Unknown	Unknown	No mapping	CT angiography (64-row detector); images were reconstructed by unknown operator(s) and were interpreted by the operating surgeon.
Uppal 2009[49]	Belgium	Prospective	34	Unknown	Unclear	Unclear	Duplex ultrasonography performed and interpreted by unknown operator(s)	CTA methodology not described
Vargas 2016[50]	USA	Retrospective	778	50	Unclear	~4:3	No mapping	CTA methodology not described

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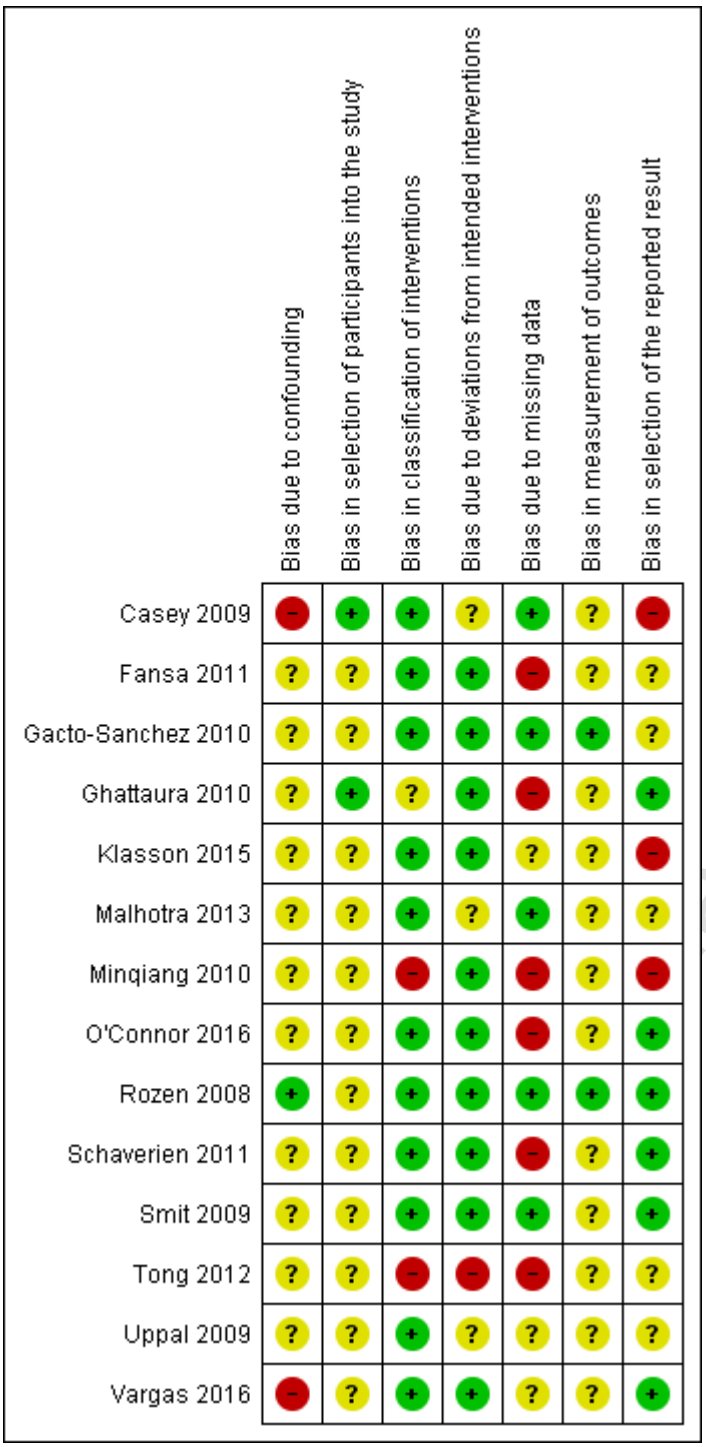


Figure 6.png

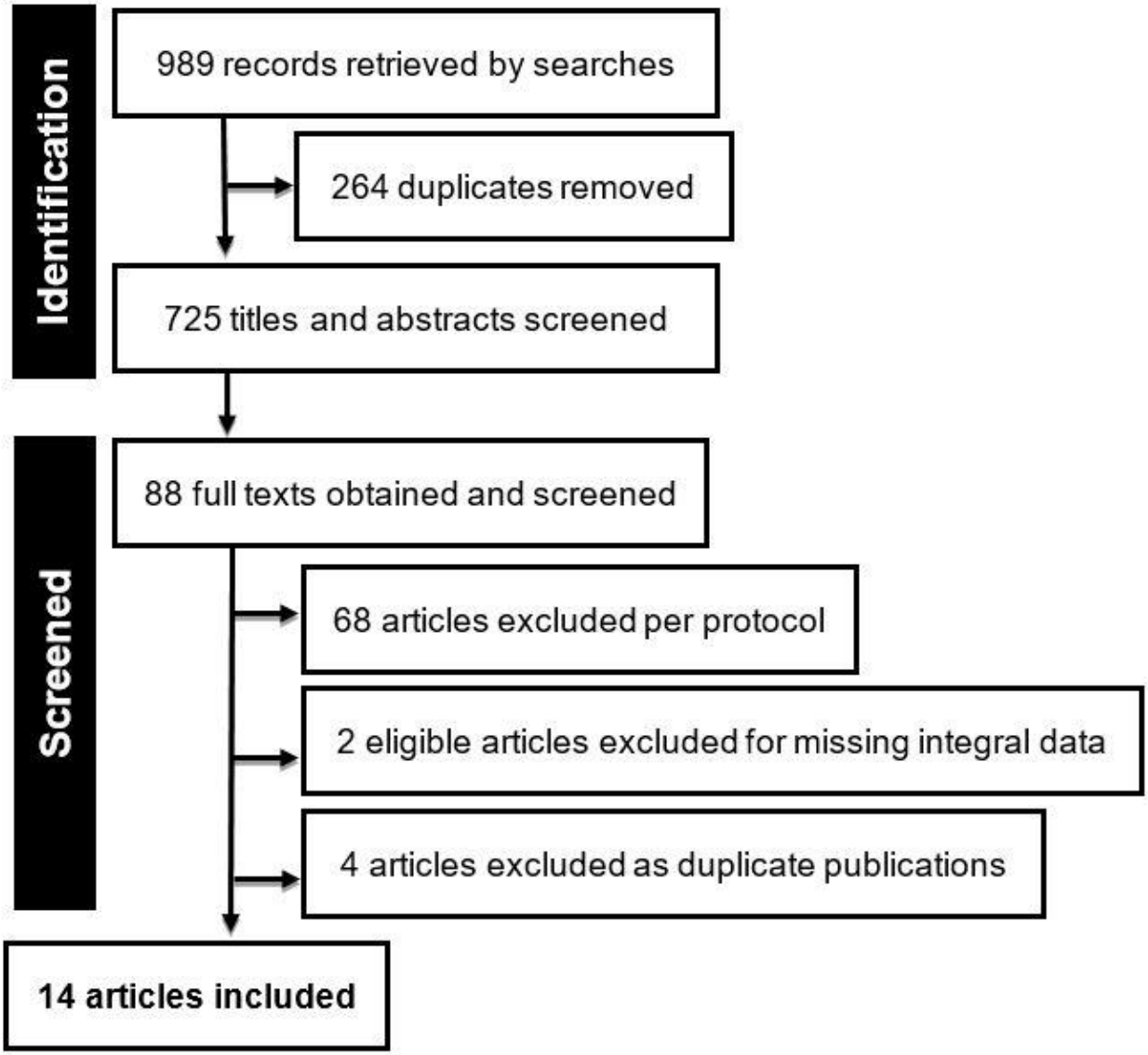


Figure 1.JPG

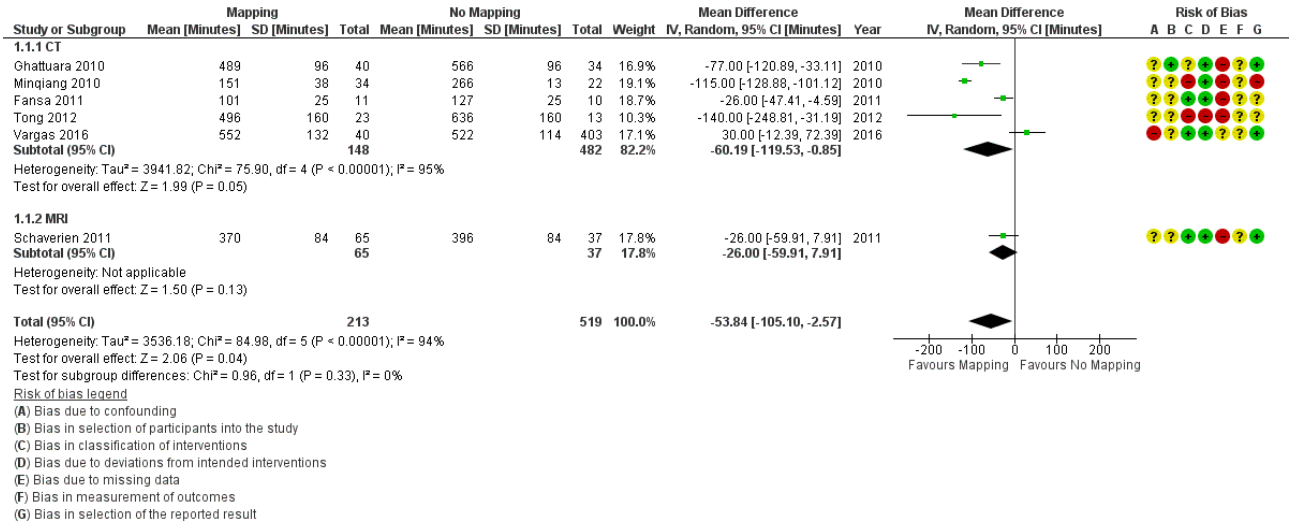
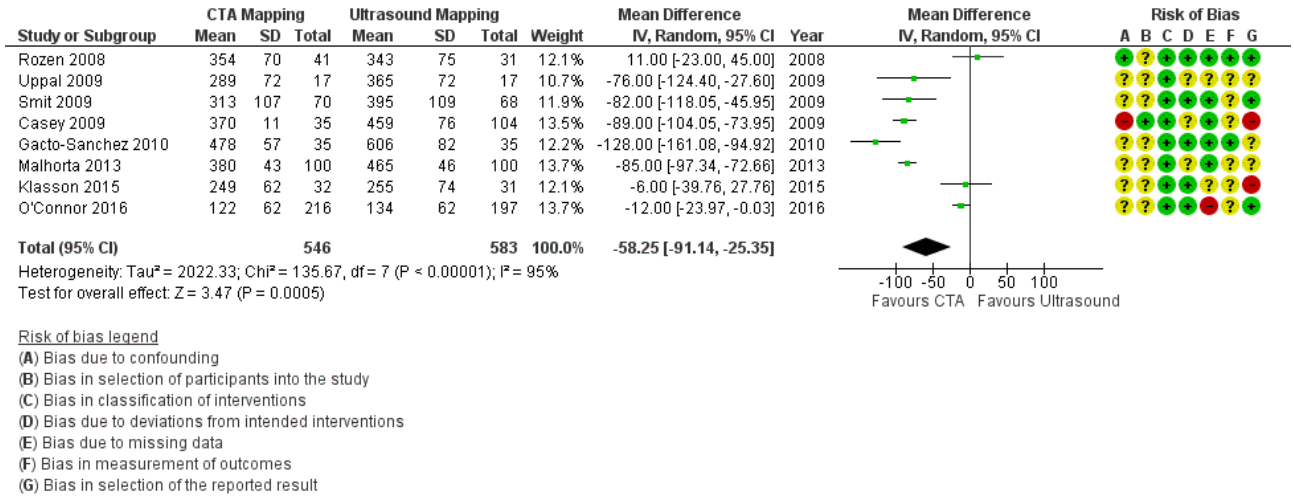


Figure 2 - Mapping v no mapping.png



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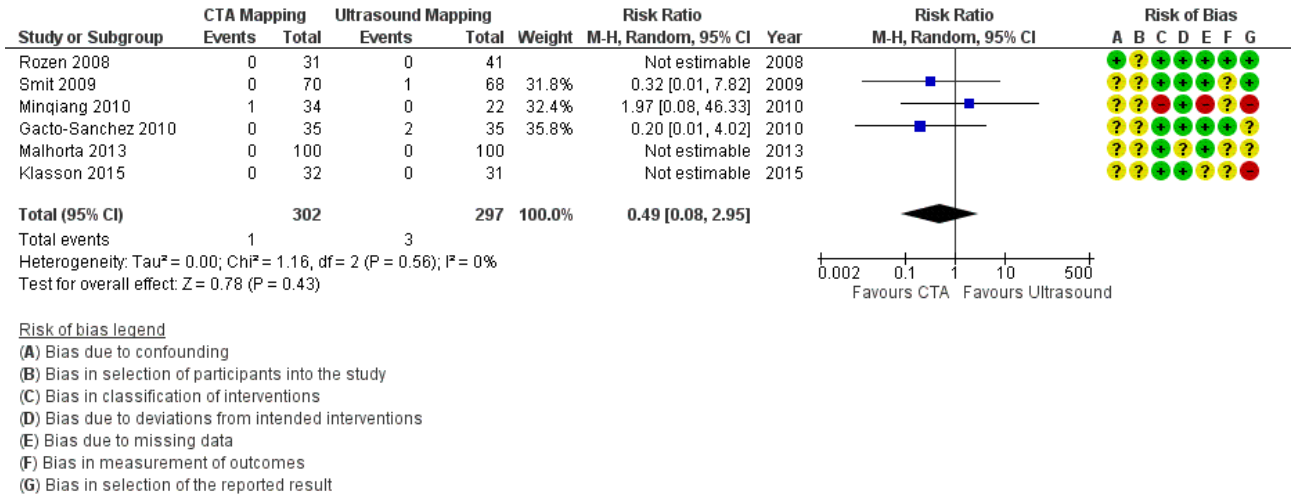

Figure 4 - total flap failure.png

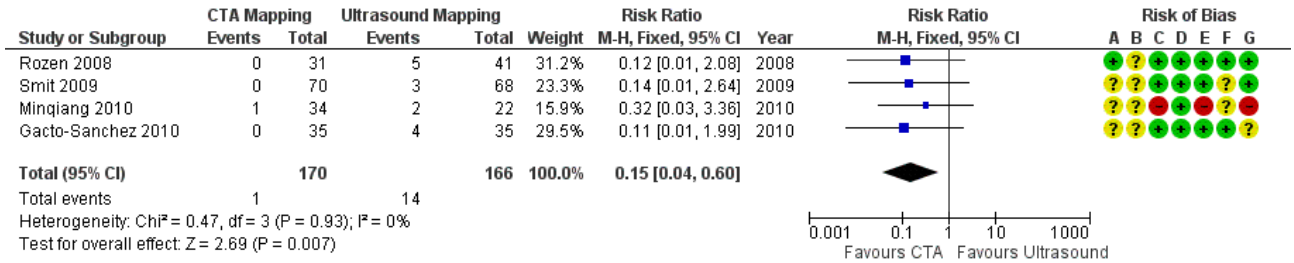

Figure 5 - partial flap failure.png