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Minimal access oesophagectomy: Systematic review and sub-group meta-analyses based on Randomised Controlled trials

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ABSTRACT

Background: All studies conducted to compare minimal access oesophagectomy (MAO) with open oesophagectomy (OO) till date, have the limitation that they are primarily bas ed on non randomized studies. Only evidence based on randomised controlled trials (RC Ts) can establish MAO as the preferred surgery for resectable oesophageal cancer (OCA) and hence the current review.

Objectives: This review aims to establish a firm body of evidence in support of MAO. The objectives involve using PICO strategy and searching for relevant RCTs, extracting and analyzing data from them in order to derive conclusions that help establish evidence in favour of MAO.

Data Sources: of the current review are RCTs that asess outcomes of MAO.

Review Methodology: Quantitave study has been designed through a systematic review and meta-analyses of RCTs.

Results: Blood loss during surgery, post -operative pulmonary infection and duration of hospital stay favour MAO versus OO for resectable OCA management.

Conclusion:The ideal MAO strategy may involve thoracoscopic oesophagectomy in prone position with low tidal volume ventilation, perioperative administration of amino-acids and neutrophil elastase inhibitor plus immediate postoperative chest physiotherapy and enteral feeding.

Keywords: *Minimal access oesophagectomy, Minimally invasive esophagectomy, Thoracoscopic oesophagectomy.*

INTRODUCTION

Oesophageal cancer (OCA) is the cancer of the food pipe/gullet. It is the eighth common est tumour (Cancer Research UK, 2016) (Appendix 1) contribution being 4.9% (Cancer today IARC, 2012). The incidence of oesophageal adenocarcinomas has quadrupled from 1960s to 1990s (Appendix 2) but the 5 year survival still remains less than 14% (Enzinger and Mayer, 2003). Only one-third of OCA patients at the time of diagnosis have resectable tumour (AJCC TNM stage cT1-3 N0-1 M0) that is suitable for surgery (Appendix 3). 30% of these also end up with microscopically residual disease. Curative surgery involves resecting part or whole of the oesophagus (Oesophagectomy) with restoration of continuity of the gastrointestinal tract subsequently (Park et al., 20 09). Traditionally open technique has been used to perform oesophagectomy. It causes substantial morbidity plus mortality. Increasing incidence of OCA and poor surgical out comes using open oesophagectomy (OO) lead to attempts to use minimal access surgical techniques instead (Smithers et al., 200 7). Minimal access surgery was found to be feasi ble for resectable OCA (Yamamoto et al., 2013). But some reluctance to use MAS instead of OO has continued till date for fear of inadequate oncological surgical resection of the advanced OCA (Titcomb et al., 2016). Currently only 16% oesophagectomies in UK are performed using MAS, the rest are open

surgeries (Burdall et al., 2016). The main reason is that level 1 evidence in favour of MAS versus OO has not been provided till date. This can be obtained only through RCT based systematic review showing outcomes in favour of minimal access oesophagectomy (MAO) versus OO outcomes (Yamamo to et al., 2013).

BACKGROUND

What is known (including any reviews) about the topic so far?

Open oesophgectomy (OO) was the only known curative surgery for OCA till 1980s when laparoscopy and thoracoscopy were introduced. Cushieri *et al*. performed and described the first MAO in 1992 (Cuschieri, Shimi and Banting, 1992). More than 2 decades later, MAO is still not as popular as other MAS procedures. It continues to be regarded as the most complex gastrointestinal surgery. Surgeons reluctant to use MAO in place of OO debate about mortality, morbidity, oncological radicality as well as the cost involved (Nagpal et al., 2010). Clear proof of superiority of MAO over OO is not forthcoming since comparative studies till date are mostly unmatched patient cohorts. The evidence that has accumulated over the years began with Collard *et al*. in 1993 who attempted subtotal oesophagectomy by thoracoscopy and showed that thoracoscopic oesophageal resections can be as extensive as open (Broussard et al, 2016). Luketich et al in 2003 reported that MAO is associated with lower mortality and shorter hospital stay than OO (Kim et al., 2012). Rajan et al. reported their results after performing MAO in 463 patients from 1997 to 2009. Their statistics included operative mortality and overall morbidity . They used various MAO techniques and concluded that MAO is safe and the type of MAO needs to be tailored depending on the OCA level, stage and histology (Senthilna than et al., 2010). Nguyen et al reported their results after 104 MAOs from 1998 and 2007 that included thoracoscopic as well as laparoscopic MAOs. They concluded that MAO is feasible, has acceptable morbidity, is associated with lower conversion rates and lower mortality as compared to OO (Nguyen et al., 2008). Blood loss ,duration of in-hospital stay and ICU stay, overall complications as well as pulmonary complication rates are less in patients having MAO vs OO (Verghese et al., 2009). The limitations of this study were heterogeneity with regards to MAO techniques, selection bias and publication bias. Biere et al. conducted a meta-anal ysis that included one controlled clinical trial and 9 case-con trol studies (Biere, Cuesta and van der Peet, 2009). Nagpal et al., conducted a meta-analy sis comparing open and minimal access oesophagectomies and the results were same as those found by Verhages et al(Nagpal et al., 2010). The results of studies comparing MAO and OO were summarised in a table (Appendix 4) by Kimet al in 2012 in their study.
All the above authors reached the same conclusion from their studies that MAO is feasi bile and safe surgical option for OCA management and comparable to OO. But the qual ity of their studies was poor. These studies are not best quality evidence to establish sup eriority of MAO over OO because they are predominantly based on case series which are regarded as low level evidence in the medical field. The authors have not compared open and minimal access oesophagectomies adequately. The studies are heterogenous with reg ard to the types of MAOs used hence lack generalizability. The studies have used various combinations of MAS and open techniques all of which contribute to heterogeneity. There is selection bias also as the patients selected for MAS were not representative of the general OCA patients. Publication bias may also be there.
The limitation of all the systematic reviews and meta-analyses conducted to compare MAO with OO is that they are primarily based on non randomized studies. These meta- analyses came to the same conclusion that that prospective randomized controlled trials (RCTs) comparing MAO and OO are needed. Only evidence from a systematic review based on RCTs can establish MAO as the preferred surgical option for resectable OCA management.

What this review may add? The current review aims to gather high quality evidence in favour of MAO by analyzing all available RCTs that assess factors affecting the outcomes of MAO. The purpose of the review is not only to collect evidence that supports MAO but also to determine the best MAO strategy for OCA resection as MAO can be performed in conjuction with differing perioperative set-ups and by using combination of different techniques. Choosing the best combination in a given scenario is important to get opti mal surgical outcomes. This review aims to find the MAO strategy that will provide best possible surgical outcomes for resectable OCAs. So, all RCTs in which factors affecting any outcome of MAO are discussed have been included. MAO may involve

thoracoscopy or laparoscopy or both or even robotic surgery. The patient positions in which MAO can be performed also vary and the results of MAO get affected by administration of different perioperative substances. Whether the patient receives neoadjuvant/adjuvant treatment, whether postoperative chest physiotherapy and enteral nutrition are given or not plus what tidal volume is given by the anaesthetist during MAO, all can affect the outcomes of MAO. Hence the RCTs involving these topics have been included in this review. This revi ew is important since all the reviews and meta -analyses till date have been based on non -randomised studies which makes current evidence in favour of MAO of low quality.

AIMS & OBJECTIVES:

The current review **aims** to establish a firm body of evidence in support of MAO for rese ctable OCA management. The review is based on the hypothesis that MAO is associated with statistically significant lower morbidity than OO. The optimal surgical technique for OCA needs to be determined by assessing all the factors which play a role in the MAO out comes . MAO can be advocated as the gold standard in management of resectable OCA by providing level 1 evidence based on RCTs. This can lead to improvement in the outco mes of OCA surgery which has been notorious for high morbidity. The **objectives** of the current study were planned using PICO framework:

P=Population= Oesophageal cancer patients

I= Minimal access oesophagectomy/perioperative modifying factors

C= Control=Open oesophagectomy/absence of perioperative modifying factors

O= MAO outcomes including primary and secondary outcome measures.

The **objectives** are:

- search for relevant RCTs as per the search strategy in the review protocol, -extraction of relevant information from the selected trials about outcomes/factors affecting outcomes of MAO,
- analysis of the information thus obtained and
- discussion of the results in order to establish all available current evidence regarding the outcomes of MAO which may used to develop the ideal MAO protocol for resectable OCA management.

The study was conducted keeping in mind the PRISMA statement [APPENDIX 5].

Methodology & Protocol

STUDY DESIGN -Basis of choosing the design of the current study & justification of met hodology used: In 2009, a survey involving surgeons in 41 countries was carried out to determine the preferred surgical option for OCA management. It was found that 52% of responders preferred open thoracotomy, 26% preferred transhiatal oesophagectomy and just 14% chose MAO. This proved that MAO was still very far from being adopted as surg ery of choice in OCA management (Boone et al., 2009). Authors of case series, case contr olled studies, cohort studies, systematic reviews and meta-analyses comparing MAO with OO have accepted in the conclusions that because of non-availability of high quality evi dence through prospective RCTs, superiority of MAO versus OO cannot be established (Dantoc, Cox and Eslick, 2012b). **L**evel 1 evidence from systematic review of randomised controlled trials is considered the gold standard of medical knowledge (Hau ghom and Advisor, 2015). This is what has been lacking so far. To prefer MAO in resect able OCA management it is essential to generate level 1 evidence through a systematic review of RCTs that report in favour of MAO versus OO. Hence the current study design is systematic review of the relevant RCTs. All the selected RCTs were found to involve qu antitative data. The information from these trials needs to be analyzed and results obtain ed need to be combined in order to determine the best MAO strategy for managing resec table OCA. So, this systematic review concludes with a meta- analyses that aim to pool the results of the selected RCTs. Study Design is a quantitative. The systematic review has a positivistic paradigm .

SEARCH STRATEGY

Database search- A comprehensive search was carried out as is needed for a systema tic review. Electronic databases searched included Biomed Central, CINAHL plus, Coch rane library, Proquest, Pubmed, Science direct, Scopus, Web of science and

Wiley. Other online sources searched included Journals (OVID journals, NHS journals library), Clini cal trial registers PROSPERO & TRIP database. The internet search results can be seen in table 1 below.

Search terms- The review needed all trials on outcomes of minimal access oesophagec tomies. So all possible synonyms of the term "minimal access oesophagectomy" were used as key words/search terms. These included :

Minimal access oesophagectomy (Mao), Minimal access esophagectomy (Mae), Minimally invasive oesophagectomy (Mi0), Minimally invasive esophagectomy (Mie), Robotic oesophagectomy (R0), Robotic esophagectomy (Re), Robot-associated oesopha gectomy (Rao), Robot-associated esophagectomy (Rae), Laparoscopic oesophagectomy (Lo), Laparoscopic esophagectomy (Le), Thoracoscopic oesophagectomy (Tho), Thora coscopic esophagectomy (The) Table 1 below has these search terms in the headings of the columns.

Search restrictions-Organisations and topic experts could also not be contacted due to time limitation for the current study. Grey literature was also not searched for the same reason. Exclusion of non-English, unpublished & gray literature induces language bias, selection bias, publication bias & location bias. Limited randomised controlled tri als on robot-assisted oesophagectomies made it impossible to include the outcomes of robotic oesophagectomies in the current study.

Journal Hand search involved looking in the university library for latest reports from health bodies, abstracts of conference presentations & reviews. But hand search was too time consuming and was abandoned.

Organisations and topic experts were not contacted due to time limitation.

Bibliography search: The reference lists of the trials selected were checked for any other relevant study.

Table 1 below- shows search results on 1 may 2016 using the keywords in the corresponding databases.

Keyword & Database	Mao	Mae	Mi o	Mie	Lo	Le	Ro	Re	Rae	Rao	Tho	The
Biomed Central	27	63	12	4	13	45	4	14	10	1	3	26
Google scholar	768	641	9420	8680	3280	13800	660	2350	2050	2190	6660	6930
MEDLINE	1	3	70	431	27	187	4	34	26	4	34	273
CINAHL	5	12	23	80	2	28	1	10	6	4	1	46
Cochrane Library	1	1	12	18	1	2	0	0	1	0	6	24
OVID Journals	805	805	1518	1518	1122	1122	332	332	388	388	263	263
Proquest central	235	796	602	1997	526	1978	121	400	282	105	346	972
Pubmed	23	23	819	819	680	680	105	105	50	50	481	481
Science direct	103	631	248	2030	297	2223	61	469	189	21	107	1023
Scopus	11	23	128	953	78	661	14	124	61	12	60	593
TRIP datab	0	0	1	17	8	13	0	3	3	0	26	135
Web of science	**8**	**20**	**145**	**1094**	**70**	**627**	**12**	**121**	**58**	**11**		216

Internet search strategy : The internet search strategy involved a scoping search first. During the scoping search, the term "minimal access oesophagectomy" was used in Goo le scholar so as to get an idea of what kind of literature is there online. Google scholar is an easily accessible and freely available database and hence the choice. This search prod uced more than 9000 results. It could be seen that there are articles, reviews and book chapters about this topic. Going through the abstracts of some articles revealed some co mmon conclusions that oesophageal cancer is a dreaded cancer for which the optimal sur gical management is still not known and there is requirement for RCT based evidence to establish the right place of MAO. Thus,the review seemed feasible and was planned to include trials only.

The initial search for this review using the keywords produced unmanagable numbers as can be seen in the table 1. Therefore the search needed to be refined.

Refined Search- The following search limits were applied:

- Search in title/abstract/keyword,
- Articles with abstracts,
- In English language,
- In humans,
- In the field of Health sciences,
- Published during the years 2000-2016,
- trials only
- Boolean operator OR,AND were used with the keywords for refined search.
- Refined search did not include Google scholar as it was impossible to apply all search limits

Refined search in following DATABASEs	T	N
[accessed through university library links in may 2016]		
[MEDLINE & CINAHL]	164	3
SCIENCE Citation Index- search via Web of Science	237	6
OVID journals (via EBSCO Host)	109	1
PROQUEST CENTRAL(4 relevant databases searched)	26	0
SCOPUS	181	1
TRIP Database	21	18
Cochrane central register of controlled trials	32	8
EMBASE via PUBMED	26	20
Refined search results [in May 2016]	796	57

Table 2

T=Total number of articles produced by the refined search in the database.

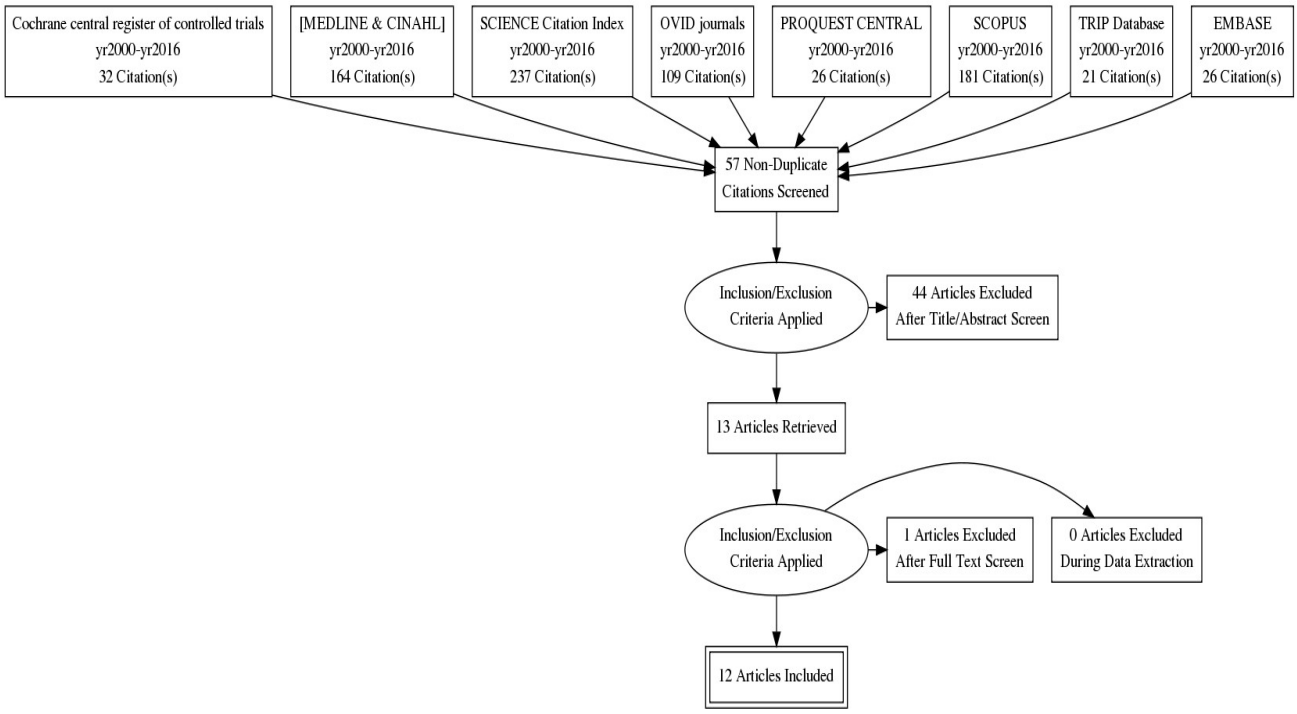
N=No. after selecting Relevant articles within each database & after removing duplicates in the particular database searched.

APPENDIX 8 at the end shows Completed search summary for EMBASE database full search to give an example of how serch was done.

Internet search strategy :(Prisma flow diagram below)

Outcome of the search process - Refined search provided total 796 articles as seen in table 2. Selection of relevant articles in each database and removing duplicates within databases brought this figure down to 57 articles. The 57 trials still included duplicates as the same articles were found in different databases. Removing duplicates and selecting trials that fitted the inclusion criteria lead to final selection of 12 RCTs for the current systematic review.

PRISMA flow diagram of refined search in the current study



These twelve selected RCTs (Bibliography/ Reference list) are in **Table 3** below**.**

Justification of the search strategy : Systematic reviews should aim to locate all studies that are relevant to the study questions. It is recommended that bibliographic searches for health care studies include databases MEDLINE and the Cochrane Central Register of Controlled Trials. Other data bases useful to search are EMBASE, CINAHL and Psych INFO (Relevo, 2012). Therefore , to locate all relevant studies for the current review, a comprehensive internet search of all the databases was carried out. Time period available to complete the review was limited and thus it was neither possible to contact experts nor to look for gray literature. All possible synonyms of the term "minimal access oesophagectomy" were used as key words /search terms because the review needed trials focussed on the outcomes of minimal access oesophagectomies. Although comparison with open oesophagectomy outcomes is involved in the meta-analysis part of the current review , the term "open oesophagectomy" or synonyms are not used as search terms. This is because comparison with open oesophagectomy was not the primary aim of the curren t review. The review aimed to study the outcomes and factors affecting the outcomes of MAO by analysis of trials done so far. The comparison with OO was obvious in five trials and thus it became possible to do a meta-analysis involving these studies. However, the rest of the trials involve comparison of different factors affecting outcomes of MAO only; this heterogeneity lead to their exclusion from meta-analysis but inclusion in the systema tic review as all of them provide valid information in relation to outcomes of MAO. The trials about MAO were published only after the year 2000 when minimal access surgery started getting popular and therefore the search limit year 2000 to current. Current me ans May 2016 for this review search. Trials only were searched as the review aims to generate high quality evidence only by studying all relevant RCTs till date

Table 3

No.	Authors	Randomised controlled trial [& what the trial assessed]
1.	Ito et al.	Thoracoscopic oesophagectomy with chest physical therapy vs open oesophagectomy with chest physical therapy [Effects on postoperative respiratory complications were studied]
2.	Ninom iya et al	Thoracoscopic esophagectomy with perioperative neutrophil elastase inhibitor versus thoracoscopic esophagectomy without perioperative neutrophil elastase inhibitor [Effects on postoperative complications were assessed.]
3.	Biere et al	Minimal access oesophagectomy versus open procedure [Postoperative Outcomes were compared]
4.	Wajed et al	Minimal access oesophagectomy with prior Gastric ischaemic conditi oning versus Minimal invasive esophagectomy without prior gastric is chaemic conditioning. [Postoperative effects on gastric conduit were asessed]
5.	Shen et al	Minimal access oesophagectomy with low tidal volume vs minimally invasive esophagectomy with conventional tidal volume [Postoperative effects on lung complications were assessed]
6	Cuesta et al	Immunological changes after minimal invasive oesophagectomy Versus Immunological changes conventional oesophagectomy
7.	Shen et al	Thoracoscopic esophagectomy in prone versus Thoracoscopic esophagectomy in decubitus position. [Study assessing how change in Ergonomics of surgery effects outcomes]
8.	Nozaki et al	JCOG0502 Thoracoscopic esophagectomy versus open esophagectomy [Study comparing outcomes & complications of thoracoscopic esophagectomy versus open oesophagectomy]
9.	Takeuchi et al	Minimal invasive esophagectomy with postoperative enteral feeding versus parenteral feeding [Study comparing postoperative complication outcomes]
10	Peet et al	Quality of life & late complications after MAO vs after OO
11.	Yama moto et al	Thoracoscopic esophagectomy with amino acid administration versus Thoracoscopic esophagectomy without amino acid adm inistration. [Study assessing effects on Postop complications]
*12.	Mariette et al	Open versus laparoscopic assisted oesophagectomy [Study comparing postoperative outcomes]

STUDY SELECTION

INCLUSION CRITERIA: RCTs meeting the following criteria were selected:

1.Completed RCTs reporting the MAO outcomes,

2.Completed RCTs reporting the MAO outcomes in comparison with OO outcomes,

3.Completed RCTs reporting results of peri-operative substances affecting MAO outcome,

4.Completed RCTs comparing different MAO techniques and their outcomes,

5.Completed RCTs reporting alteration MAO outcomes due to ny factor

EXCLUSION CRITERIA: The studies excluded were:

1.All studies that are not RCTs.

2.Trials reporting MAO outcomes but not randomized.

3.RCTs that fit inclusion criteria (as per their study protocol) but still incomplete.

4.RCTs that discuss oesophagectomy but neither report any MAO outcome nor any factor that directly or indirectly can influence any MAO outcome.

5.RCTs that compare MAO and adjuvant/neo-adjuvant chemo/radiotherapy

HOW THE INCLUSION & EXCLUSION CRITERIA WERE USED - The refined search had provided total of 796 articles from different databases. This search result was screened by reading titles. At this point abstracts were not read since it was possible by reading the titles only to exclude most of the studies as they were non RCT studies or studies that were trials but irrelevant to the current topic of interest These excluded studies mostly met the exclusion criteria 1 and 2. None of them obviously met the inclusion criteria. The exclusion by reading titles and removing duplicates within each database lead to a list of 57 studies from all databases. The term "57 non-duplicate studies" used in the PRISMA flow-chart above actually means that there remained no duplicates in indivisual database search result and search results of indivisual databases were combined to get this list of 57 articles. The duplicates were however still there in this combined result because the same study could be found in multiple databases. These 57 articles had to be screened again to remove the duplication. The abstracts were read. 24 articles were excluded as they either did not meet all inclusion criteria or they were duplicated in multiple data bases. 13 articles were identified and found to meet the inclusion criteria but when full texts of these studies were read, one article had to be excluded (Appendix 6) because it was a trial (E2202 study) reporting MAO outcomes but not involving the randomisation process. The first inclusion criteria of being a randomised controlled trial was not met. The selected 12 RCTs met either one or multiple inclusion criteria. Table 3 above provides information about what each included RCT reports.

Outcome & justification of selection process - The search strategy (with the inclusion and exclusion criteria) as described above resulted in a list of 12 RCTs. They provide authent ic information about the outcomes of MAO and factors influencing these outcomes. In evidence based medicine,PICO strategy helps formulation of the research question and aids search for literature(Schardt et al., 2007).

P	Population	Patients with histologically proven oesophageal cancer who gave written consent to have minimal access oesophagectomy
I	Intervention	Minimal access oesophagectomy
C	Comparison	Open oesophagectomy
O	Outcomes	Post operative outcomes

However only 5 of the 12 trials can be seen as comparing MAO & OO outcomes. In the re maining RCTs, intervention and comparison factors differ although the outcome report ed is one or the other outcome of MAO in every trial. The same outcome was not report ed in all the RCTs identified. So PICO for the remining RCTs is the following

P	Population	Patients with histologically proven oesophageal cancer who gave written consent to have minimal access oesophagectomy
I	Intervention	Periopertive intervention [administrtion of substance or technique change] to check effect on MAO
C	Comparison	NO intervention (CONTROL GROUP)
O	Outcomes	Post operative outcomes

Critical appraisal : Criteria used to determine quality with justification : This review included RCTs only. The appraisal process to determine the quality of RCTs may involve using tools like the Cochrane Collaboration Risk of Bias Tool (CCRBT) and Effective Public Health Practice Project Quality Assessment Tool (EPHPP) (Armijo-Olivo et al., 2010).The criteria that determine the quality of any

RCT include validity of the res ults of that trial and the usefulness of the results to the local population as per CASP (CASP,UK, 2013). Using CCRBT, EPHPP and CASP tools to assess the RCTs selected in this review, it was established that this review involves high quality studies. The results of all RCTs were found to be valid.

-Processes used to appraise studies - involved using the CASP tool first. The CASP tool assessed the quality of the selected trials in terms of whether the results of the trials are valid, what those results are and whether these results can help locally. To give a glo bal rating to each trial the EPHPP quality assessment tool for quantitative studies was used. It helped to appraise the selected studies for quality, rigour and validity. The CCR BT helped to determine the kinds of bias in the trials selected (Appendix 7). Example ; In Bierer et al, 2012 RCT, bias elimination, use of PICO strategy and randomization is sound but no blinding may reduce the quality of findings.

-Outcome of the appraisal process & how this information is used to inform the synthesis: Each study was reviewed first by CASP tool and then by EPHPP quality assesment tools and finally by CCRBT tool. The outcome of the appraisal process was th at it became possible to determine the quality of studies in terms of bias, design of RCT, any confounding factors, blindedness in the RCTs , data collection methodology used plus any drop outs. The quality assesment process also established that the results of the selected trials are valid, no low quality studies have been incorporated into the current review. This helped to synthesise high quality evidence in favour of MAO when the combining the results of the selected RCTs.

Ethical appraisal :-Processes used to establish ethical aspects of the review : Ethical approval was not needed to conduct this systematic review.

-Principles used to judge ethical quality : The selected trials were checked to con firmed that the ethical approval had been sought to carry out all the RCTs selected in the current review from the respective ethical committees/ boards wherever the trials were conducted. All patients that participated in the selected RCTs had given written informed consent for participation in the trials as needed. The ethical principle of confidentiality has been followed in all the trials. There is no risk of using information of trial participants as the patients have already provided informed consent for all trials involved.

-Outcome of ethical process appraisal: The ethical appraisal process determined that the patients who participated in the trials need not to be contacted for permission as they had all given valid written informed consent.

-Justification for the above : Generally the ethical review of research proposals is con ducted by the

Faculty Research Ethics Panel (FREP) of the university. As this systematic review did not involve any direct patient contact no ethical approval was sought. Howe ver it was ascertained that the included RCTs had the approval of respective ethical co mmittees and that makes this an ethically acceptable study.

Data extraction: The data was extracted in the form of tables [**tables 4-7**] by only one reviewer as per university assignment guidance. **No strategy** was needed to manage missing data in this review. As the review was completed by one reviewer only, there is no second reviewer for verification of data involved in this study.

Since the study aimed to assess MAO outcomes any possible risk factor needs to be addressed and therefore information was collected as follows :

1)**patient characteristics** (age, gender,BMI, ASA grade) to assess that the patient pop ulations undergoing intervention and control were comparable.

2)**intraoperative variables** (duration of operation, blood loss, anastomotic site, total lymph node retreival) were assessed to compare different MAO techniques as well as fac tors affecting them.

3)**histopathological variables** (tumour location, tumour histology ,resection achieved, tumour stage) were assessed to establish how effectively MAO can be in resectable OCA management.

4)**post-operative variables** include the primary outcomes and secondary outcomes sought in this review. These variables are defined in the

DEFINITION TABLE below.

Primary outcomes	**(2 Post-operative variables)**
Postoperative pulmonary infection	Clinical signs and symptoms of pneumonia with radiological confirmation by chest x-ray or CT scan plus positive sputum culture occuring after operation while in hospital or within one month of surgery.
Hospital stay duration	Total time patient had to spend in the hospital for and after the MAO surgery
Secondary outcomes	**(Intra-operative variables)**
Total duration of surgery	Time from skin incision to skin closure
Blood loss	Amount of blood in ml that the patient loses during the MAO operation as a consequence of the surgical procedure.
Adequate Lymph node retreival	In oesophageal cancer , 15 lymph nodes retreived is generally considered adequate lymph node retreival (Merkow et al., 2012)
Vocal cord paralysis	Clinically hoarseness/voice difficulties following surgery
Anastomotic complications	Leak or stenosis at conduit site postoperatively
Quality of life after 6 weeks post-operatively	Quality of life assessed using EORTC questionnares (Appendix 6) [European Organization for Research and treatment of cancer]

	TRIAL authors	Male OO : MAO	Female OO : MAO	* Age (years) OO : MAO	†BMI (kg/m2) OO : MAO	ASA GRADE OO : MAO
1	Biere et al	46 : 43 82% : 73%	10 : 16 18%: 27%	62 : 62 (42-75): (34–75)	24 : 25 (3·7) (3·6)	1 15 (27%) : 10 (17%) 2 32 (57%) : 34 (58%) 3 8 (14%) : 14 (24%) 4 1 (2%) : 1 (2%)
2	Cuesta et al	12 : 10	1 : 4	62:65 (52–74) : (56–75)	23 : 24 (21-33) : (16–33)	APNI
3	Peet et al	46 : 43 82% : 73%	10 : 16 18 %: 27 %	62 : 62 (42-75) : (34-75)	24 : 25 (3.7) (3.6)	1 15 (27%) : 10 (17%) 2 32 (57%) : 34 (58%) 3 8 (14%) : 14

						(24%) 4 1 (2%) : 1 (2%)
4	Nozaki et al	93:82 85.3%:81.2 P=0.462	16:19 14.7:18.8	62: 63 (41–75): (48–75) P= 0.522b	22: 23 (13-29):(17-28) P= 0.934b	APNI
5	Ito et al	20:14	0:2	58.9 ± 9.3 : 61.8 ± 8.4	APNI	APNI
6	Yamamoto et al	S:AA 51/60	S : A.A 9/10	S : A 64.56+-8.4 : 65.66+-7.7 P=0.94	S:AA 21.5+-3.2 : 21.8+-3.8 P=0. 876	ASA S:AA 1 13:12 2 22:20 P=0.93
7	Wajed et al	APNI	APNI	APNI	APNI	APNI
8	Shen et al PP:DP 35:32	PP: DP 26:24 P=.946x	PP:DP 9:8	PP:DP 60.5+-7.3: 60.9+-8.4 P=0.836t	PP:DP 23.4+-4.1:22.7+-3.9 P=0.477t	ASA PP:DP 1 13: 12 2 22:20
9	Ninomiya et al C:S	C:S 10:7	C:S 0:3	C:S 63:64 P=0.91	C:S APNI	C:S APNI
10	Shen et al (2013) PV:CV 43:48	PV:CV 40:32	PV:CV 13:16	PV:CV 60.5+_7.3: 57.2 +-9.1 P =0. 403	PV:CV	ASA PV:CV 1 20:25 2 33:23
11	Takeuchi et al	Pn:En 18:19	Pn:En 5:9	Pn:En 60.7 ± 8.97: 63.6 ± 7.13 P=0.281	Pn:En APNI	Pn:En APNI

Table 4a

Patient characteristics (? Risk factors) in RCTs **comparing OO & MAO**

The comparison is expressed as ratio in RCT column to fit the table. The abbreviations/signs are explained in text box.

Data includes n (%), median (range) and mean (SD).	OO=open oesophagectomy,
†Normal distribution, Independent Samples t test applied	MAO=minimal access oesophagectomy.
BMI=body-mass index.	ASA=American Association of Anesthesiologist
*Skewed distribution, Mann-Whitney test applied	*Skewed distribution, Mann-Whitney test applied
P=fishers exact test	B=Wilcoxon rank sum test
APNI=Authors provide no information	

Table 4b Patient characteristics (? Risk factors) in RCTs studying factors affecting MAO outcomes

The factor studied versus control (expressed as ratio) has been abbreviated to fit the table.The abbreviations are explained in the text box and are used in subsequent boxes also

DP= Decubitus position oesophagectomy	PP=prone position oesophagectomy
APNI=Authors provide no information	CV= Controlled conventional tidal volume ventilation
C= controls receiving saline x=x2 test	S=Sivelestat sodium hydrate group
Pn= Parenteral nutrition	t=student t-test En= Enteral nutrition
S: AA = Saline : Amino acid	PV = Preserved low tidal volume ventilation
Nm=Neoadjuvant therapy+MAO	Om=Only MAO m= MAO
N+m -neoadjuvant treatment +MAO	

Table 5a Histopathological characteristics tumours

RCT authors	Biere et al	Cuesta et al	Peet et al	Ito et al	Nozaki et al
	OO:MAO	OO:MAO	OO:MAO	OO:MAO	OO:MAO
Tumour location in oesophagus Upper Middle Lower	3 :1 22:26 31:32	APNI	3:1 22:26 31:32	APNI	12:15 p=0.18 65:59.6 32:19

Tumour type ACA SCCA Others	36:35 19:24 1:0	11:13 p=ns 2:1 p=ns	36:35 19:24 1:0	APNI	APNI
Noeoadjuvant Chemoradioth Chemoth	52:54 4:5	APNI	52:54 4:5	APNI	Definitive ChemoRTH 159:
STAGE 0 I IIa IIb III IV	0:1 4:4 16:17 6:9 14:11 5:4	APNI	0:1 4:4 16:17 6:9 14:11 5:4	APNI	APNI
No residual nodes	7:9	APNI	7:9	APNI	APNI
Resection margin R0 R1	47:54 5:1	APNI	47:54 5:1	APNI	APNI

RCT authors	Yamamato et al	Wajed et al	Shen et al (2014)	Takeuchi et al	Shen et al (2013)	Ninomiya et al
	S : AA		PP:DP	Pn:en	PV:CV	C:S
Tumour location U In M esophagus LOG	APNI	APNI	6:5 22:20 7:7	APNI	7:10 38:31 8:7	3:2 4:5 3:4

Tumour type ACA SCCA Others	APNI	APNI	2:3 33:29 p=0.917	APNI	3:2 50:46 P=.909	APNI
Noeoadjuvant Treatment Chemoradioth Chemoth	APNI	APNI	APNI	P=0.658 13:12	APNI	APNI
STAGE 0 I IIa IIb III IV	P=0.72 33:40 13:9 14:21 0:0	APNI	APNI	P=0.469 11:10 7:6 3:4 2:4	P=.86 7:5 11:9 35:34	P=0.572 0:0 4:2 4:5 0:3 2:0
No residual Lymph nodes	APNI	APNI	APNI	APNI	APNI	APNI
Resection margins R0 R1	APNI	APNI	APNI	APNI	APNI	APNI

Table 5b- Histopathological characteristics tumours

The tables hereafter only contain mean/median values.This was done to simplify the ratios.The range/2SD are given in the RCTs for some of these variables.

Table 6a Intraoperative data of the studies comparing OO:MAO

Intra-operative data	Biere et al OO:MAO	Cuesta et al OO:MAO	Peet et al OO:MAO	Nozaki et al OO:MAO
Surgery time (in	299:32	266:305	299:32	399:510

minutes)*t	9 P=0.002	P=ns	9 P=0.002	P<.001b
Blood loss (in mL) t	45:200 P<0.001	450:275 P=.045	45:200 P<0.001	412:293 P<.001b
Anastomotic Level - cervical - thoracic	37:38 15:17	APNI	37:38 15:17	APNI
Total lymph nodes retreived	21:20 P=0.852	19:19 P=ns	21:20 P=0.852	47:56 P=0.063

s= student t-test	b=Wilcoxon rank sum test
*-time from skin incision to closure,	t= skewed distribution,
Data includes median (range) or mean (SD)	

Table 6b Intraoperative data in studies on factors affecting MAO outcomes

Intra-operative data	Yamamoto et al S:AA	Shen et al (2013) CV:PV	Ninomiya et al C:S	Shen et al (2014) PP:DP	Takeuchi et al (2015) Pn : En
Surgery Time (minutes)	374:365 P=0.29	214:195.8 P=0.338*	549:517 P=0.393	Th 68 :87 p<.001s Ab 55: 51, p.397	548:564 P=0.395
Blood loss (mL)	210.2:168.8 P=0.75	130:170 P=.728t	320:305 P=0.796	89:67 p<.001s	211:20 P=0.616
Anastomosis level	APNI	APNI	APNI	APNI	APNI
Total	APNI	APNI	APNI	18.2:15.4	67:77

lymph nodes retreived				P<.001s	P=0.053

Table 6c Intraoperative data in studies on factors affecting MAO outcomes

	Trial authors	
1.	Ito et al	The intra-operative details in this trial are: OO: MAO Vital capacity (l) 3.75:3.50 Vital capacity (%) 109.3:107.8 FEV1 2.88:2.60 FEV1(%) 81.0:82.3 Peak expiratory flow (l/s) 7.95:7.08 {only mean values given here}-no statistically differences noted by authors
2.	Wajed et al	Only data about conduit perfusion is available in this trial.

Table 7a- Postoperative data

1.	Ito et al	OO : MAO Improved Vital capacity 1347 : 1325 [in ml] Improved Mean FEV1 1028 : 951 [ml/kg] Mean Peak expiratory flow 2.51: 2.61 (improved) No. of patients with Level 3Coughing ability 8:6 [fev1>10 ml/kg body weight] 3:1 [fev1<10 ml/kg body weight] [statistics on DAY 3 Post-op post chest physical therapy]
2.	Wajed et al	MAO without ligation :MAO with ligation **Perfusion coefficient (mean)** 38.3+- 12 : 37.7+-16.8 **at the gastric conduit** p= 0.798 Mann Whitney U-test used

3.	Peet et al	Questionnares used to assess: SF36 EORTC C30 EORTC OES 18 Quality of Physical Global Pain life p=0.003 health domains At 1 year p=.020 at 6 weeks p=.002 at 6 weeks p=.042 at at 1 year p=.003 at 1 year EORTC=European Organization for Research and treatment of cancer

TABLE 7B Post-operative Data

	Biere et al OO:MAOp value	Cuesta et al OO:MAOpvalue	Nozaki et al OO:MAO pvalue	Ninomiya et al C:S
ICU stay [days] t	1 :1 P=0.06	1:1 P=ns	-	3.10:2.66 P=0.481
Length of stay	-	-	24:24 p=0.472	31:32 p=0.853
VAS [10 DAYS] L	3:2 P=0.001	APNI	-	APNI
Epidural failure	11:10 P=0.734	APNI	-	APNI
Pulmonary infection in hospital	19:7 P=0.005	1:0 p=ns Empyema	24:11 p=.041 Atelectasis	1:1 {PNEMONIA}
Pulmonary embolism	0:1 P=0.328	0:1 P=ns		APNI
Anastomotic leakage	4:7 P=0.390	1:3 p=ns	15:7 P=0.12	APNI
Other ** complications	2:2 P=0.958	APNI	4:2 p=0.684 intravascular catheter infection 2:3 p=0.673 paralytic ileus 0:4 p=.052 intestinal obstruction	SIRS 49:17 P=0.009

			5:16 p= .01 Other complications	
Vocal cord paralysis e	8:1 P=0.012	2:1 P=ns	17:15 P=1 recurrent nerve paralysis	U/L 3:3 B/L 6:5
Re-operations	6:8 P=0.641	APNI	2:10 P=.016	APNI
30-day mortality	0:1	0:1 P=ns	-	APNI
In-hospital mortality	1:2		1:1 p=1	APNI

			U/L Unilateral
** means those thoracic complic ations not related to mediastinitis, empyema, hiatus hernia,	L= Linear mixed model P= p value B/L Bilateral	t-Skewed distribution	P value calculated byFishers exact test in Nozaki et al study
chylous leak needing re-operation	e=endoscopically	confirmed	ns=not significant

Table 7c Post-operative data	**Shen et al (2013) PV:CV**	**Takeuchi et al Pn:En**	**Shen et al (2014) DP:PP**	**Yamamoto et al S:AA**
Rate of weight loss at day 14 Postop		5.05:2.94 P=0.02	APNI	APNI
Pneumonia	5: 13 P=.021 Pulmonary complications	7:3 p=0.137	2:4 p=0.587 [pulmonary Complication]	18:10 p=.029 Surgical Infectious complicatio ns
Atelectasis		2:2 p=0.965	See above	
Recurrent laryngeal nerve palsy	4:13 p=0.891 Hoarseness		3:2 p=0.917 [hoarseness]	13:6 p=0.86 Non-infectious surgical complicatio ns

Anastomotic leak	7:5 P=.952	4:5 p=0.767	3:3 p=0.754 f	
Postop hospital stay		27.1:28.3 P=0.147	APNI	
ICU stay			APNI	
Mortality	0:0		0:0	0:0

F=fisher exact test

	RCT specific post-operative
Shen et al {2014}	Ergonomic Eye blink rate DP:PP p<0.001 for R2 and R1-R2 Evaluation MSS scores DP:PP p<0.001 R=rate of eye blink/mniute of surgeon at beginning [R1] & end [R2]
Shen et al [2013]	Pulmonary complications are significantly lower in the group that receive lower tidal volume plus PEEP than those who receive conventional tidal volume

Mariette et al, 2016 *	Open oesophagectomy	Hybrid minimal invasive oesophagectomy
Patients no.	104	103
Major post-operative morbidity p=.0001	67	37
Major pulmonary complication p=.03	31	18
30 day mortality	5	5

Data analysis - The data is quantitative and therefore statistics software was needed. Factors affecting the MAO outcomes were found to be independant and this made it impossible to analyze all the data together in a meta-analysis. The meta-analysis was possible for sub-group of few trials in which there was direct comparison of MAO and OO outcomes. In order to measure variability in the data sets obtained from the RCTs, standard deviation was first calculated for all patient numbers in the selected RCTs using online statistics calculators(table below).

STANDARD DEVIATION OF MEAN & CONFIDENCE INTERVALS

		I	C	T	M	SD	Popu SD	V M SD	V popu SD	CI
1	Biere et al	59	56	115	57.5	2.12	1.5	4.5	2.25	0.39
2	Cuesta et al	14	13	27	13.5	0.71	0.5	0.5	0.25	0.27

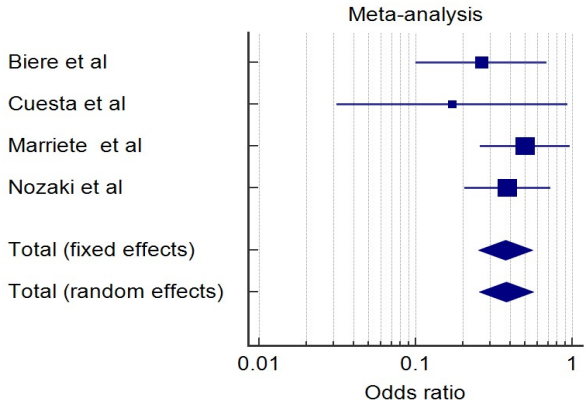
3	Peet et al	59	56	115	57.5	2.12	1.5	4.5	2.25	0.39
4	Nozaki et al	101	109	210	105	5.66	4	32	16	0.77
5	Yamamoto Et al	70	60	130	65	7.07	5	50	25	1.22
6	Shen et al (2013)	53	48	101	50.5	3.53	2.5	125	6.25	0.69
7	Ninomiya et al	11	11	22	11	0	0	0	0	-
8	Shen et al (2014)	35	32	67	33.5	2.12	1.5	4.5	2.25	0.51
9	Takeuchi etal	24	23	47	23.5	0.71	0.5	0.5	0.25	0.2
10	Ito et al	14	22	36	18	5.66	4	32	16	1.85
11	Wajed et al	8	8	16	8	0	0	0	0	-
*	Marriette et al	103	104	207	103.5	0.71	0.25	0.5	0.5	0.2

Calculations through online statistics calculators [easycalculation.com/statistics/standard-deviation.php/](mccallum-layton.co.uk/tools/statistic-calculators)

ABBREVIATIONS USED above	M= Mean No-number, C=Control,CI= confidence interval
V= Variance R= Range for the true popu M	SD=Standard deviation of mean upto 2 decimal
popu=Population , I=Intervention	**Secondary outcomes**
Primary outcomes Postoperative pulmonary infection (PPI) Hospital stay duration (HSD)	Total duration of surgery= TDS, Blood loss=BL, lymph node retreival= LNR, Vocal cord paralysis=VCP, Anastomotic complications=AC

Methods used for analysis with justification: To integrate the quantitative findings from similar although separate RCTs , meta-analysis was performed. Continuous measure meta -analysis was used because range was available in the data of others besides the mean value of variable. In this review, the meta-analyses involve only few RCTs because the out comes and intervention/control were comparable only in few RCTs. Where range of variable was given the standard deviation of variable was used based on the formula [that is standard deviation is approximately highest value minus lowest value divided by 4 (Taylor,2016)]. In RCTS without range of variable and only mean values, Odds ratio meta-analysis was performed. MedCalc software was used for meta-analysis of all primary and secondary outcomes as it is easy to install plus reliable to use. A forest plot and table for each outcome analyzed was generated during the meta-analysis as seen below.

Postoperative pulmonary infection



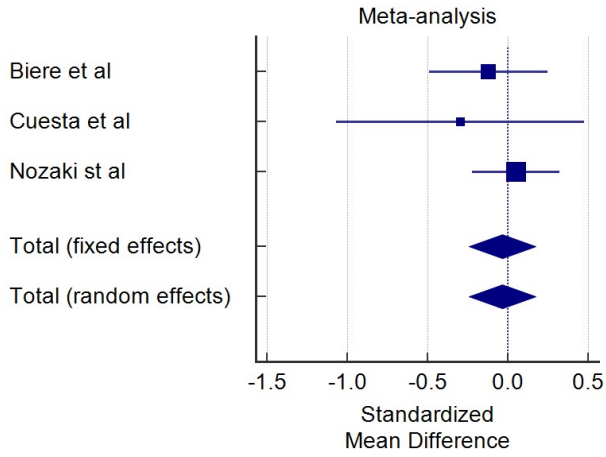
1. Intervention groups		2. Control groups	
Variable for total number of cases	MAO	**Variable for total number of cases**	OO
Variable for number of positive cases	PPI	**Variable for number of positive cases**	OOPPI

Test for heterogeneity	
Q	2.0812
DF	3
Significance level	P = 0.5557
I^2 (inconsistency)	0.00%
95% CI for I^2	0.00 to 81.39

Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%) Fixed	Weight (%) Random
Biere et al	7/59	19/56	0.262	0.100 to 0.687			17.29	17.29
Cuesta et al	3/14	8/13	0.170	0.0312 to 0.930			5.58	5.58
Marriete et al	18/103	31/104	0.499	0.258 to 0.965			36.90	36.90
Nozaki et al	19/101	41/109	0.384	0.204 to 0.723			40.23	40.23
Total (fixed effects)	47/277	99/28	0.377	0.253 to	-	<0.001	100	100

		2		0.562	4.795		.00	.00
Total (random effects)	47/277	99/282	0.378	0.253 to 0.565	- 4.753	<0.001	100.00	100.00

Hospital stay duration



Variable for studies	Study		
1. Intervention groups		**2.Control groups**	
Variable for number of cases	MAO	**Variable for number of cases**	OO
Variable for mean	HSD	**Variable for mean**	OOHSD
Variable for SD	SD	**Variable for SD**	OOHSD_SD OOHSD-SD

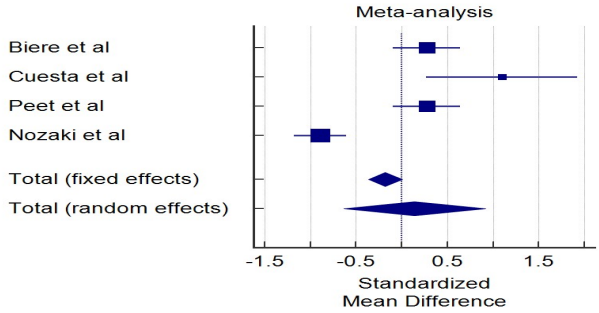
Test for heterogeneity

Q	1.0764	**I^2 (inconsistency)**	0.00%
DF	2	**95% CI for I^2**	0.00 to 93.77
Significance level	P = 0.5838		

Study	**N 1**	**N 2**	**Total**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%) Fixed**	**Weight (%) Random**
Biere et al	59	56	115	-0.121	0.185	-0.489 to 0.246			32.68	32.68
Cuesta et al	14	13	27	-0.298	0.376	-1.072 to 0.476			7.97	7.97

Nozaki st al	101	109	210	0.0486	0.138	-0.223 to 0.320			59.36	59.36
Total (fixed effects)	174	178	352	-0.0346	0.106	-0.243 to 0.174	-0.326	0.745	100.00	100.00
Total (random effects)	174	178	352	-0.0346	0.106	-0.243 to 0.174	-0.326	0.745	100.00	100.00

TOTAL DURATION OF SURGERY



Test for heterogeneity

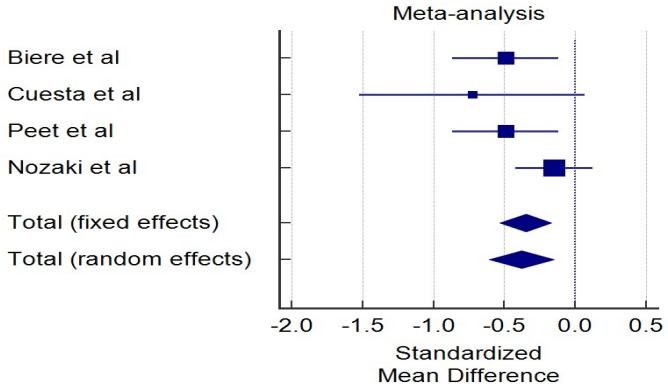
Q	46.1175
DF	3
Significance level	P < 0.0001
I^2 (inconsistency)	93.49%
95% CI for I^2	86.54 to 96.86

Study	N1	N2	Total	SMD	SE	95% CI	t	P	Weight (%) Fixed	Weight (%) Random
Biere et al	59	56	115	0.272	0.186	-0.0971 to 0.641			25.78	25.98
Cuesta et al	14	13	27	1.097	0.402	0.269 to 1.925			5.52	21.45
Peet et al	59	56	115	0.272	0.186	-0.0971 to 0.641			25.78	25.98
Nozaki et al	101	109	210	-0.891	0.144	-1.175 to -0.606			42.91	26.59
Total (fixed	233	234	467	-0.182	0.094	-0.367 to	-1.92	0.0	100	100.0

effects)					5	0.00425	0	55	.00	0
Total (random effects)	233	234	467	0.140	0.395	-0.637 to 0.916	0.353	0.724	100.00	100.00

Intervention group		**Controls group**	
Variable for no of cases	MAO	Variable for no of cases	OO
Variable for mean	TDS	Variable for mean	OO-TDS
Variable for SD	TDS-SD	Variable for SD	oo-TDS_SD
TDS=Total duration of surgery	MAO OO	Minimal access oesophagectomy Open oesophagectomy	SD Standard deviation

BLOOD LOSS



Test for heterogeneity

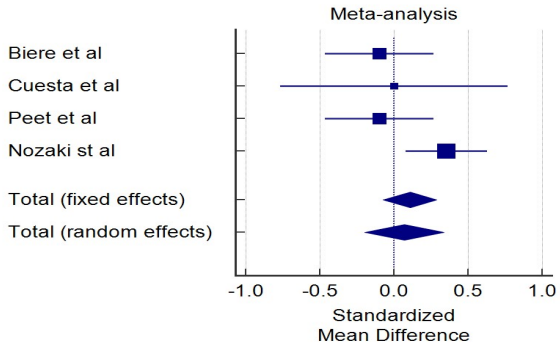
Q	4.2365
DF	3
Significance level	P = 0.2370
I^2 (inconsistency)	29.19%
95% CI for I^2	0.00 to 74.01

Study	**N1**	**N2**	**Total**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%) Fixed**	**Random**
Biere et al	59	56	115	-0.492	0.188	-0.865 to -0.119			24.38	26.45
Cuesta et al	14	13	27	-0.726	0.386	-1.522 to 0.0693			5.78	8.22

Peet et al	59	56	115	-0.492	0.188	-0.865 to -0.119			24.38	26.45
Nozaki et al	101	109	210	-0.148	0.138	-0.420 to 0.123			45.45	38.89
Total (fixed effects)	233	234	467	-0.349	0.0929	-0.532 to -0.167	-3.761	<0.001	100.00	100.00
Total (random effects)	233	234	467	-0.378	0.116	-0.607 to -0.149	-3.242	0.001	100.00	100.00

Intervention group		**Controls group**	
Variable for no of cases	MAO	Variable for no of cases	OO
Variable for mean	BL	Variable for mean	OO-BL
Variable for SD	BLSD	Variable for SD	00BLSD
BL=Blood Loss	MAO OO	Minimal access oesophagectomy Open oesophagectomy	SD Standard deviation

LYMPH NODE RETREIVAL



Study	**N 1**	**N 2**	**Total**	**SMD**	**SE**	**95% CI**	**t**	**P**	**Weight (%)**	
									Fixed	**Random**
Biere et al	59	56	115	-0.0981	0.185	-0.466 to 0.269			24.79	27.18
Cuesta et al	14	13	27	0.000	0.373	-0.769 to 0.769			6.11	10.72
Peet et al	59	56	115	-0.0993	0.185	-0.467 to 0.268			24.79	27.18

Nozaki st al	101	109	210	0.353	0.139	0.0800 to 0.627		44.31	34.92
Total (fixed effects)	233	234	467	0.108	0.0923	-0.0737 to 0.289	1.166	0.244	100.00	100.00
Total (random effects)	233	234	467	0.0697	0.136	-0.198 to 0.338	0.511	0.609	100.00	100.00

Test for heterogeneity

Q	5.7017
DF	3
Significance level	P = 0.1271
I^2 (inconsistency)	47.38%
95% CI for I^2	0.00 to 82.54

Variable for studies	Study		
1. Intervention groups		**2. Control groups**	
Variable for number of cases	MAO	**Variable for number of cases**	OO
Variable for mean	LNR	**Variable for mean**	OOLNR
Variable for SD	SD	**Variable for SD**	OOLNR_SD

Methods used for meta-analysis: MedCalc Software is used for meta-analysis in the current review. It utilises Mantel-Haenszel method given by Mantel & Haenszel in 1959 in order to calculate the odds ratio. The model used by MedCalc during odds ratio based meta-analysis is fixed effects model (Schoonjans, 2016).

Investigation of heterogeneity:The random effects model is used by MedCalc to incorporate heterogeneity. Therefore, the summary odds ratio can be derived(DerSimonian & Laird, 1986) while performing met a-analysis using MedCalc Software. Cohran's Q and I^2 can be seen as measures of heterogeneity in all the meta-analysis in this review.Cohran's Q detects heterogeneity (Higgins et al., 2003) and I^2 represents the percent of observed total variation across all studies which may be because of real heterogeneity rather than chance (Stats Direct Limited, 2000).

Comparisons undertaken: The primary and secondary outcome variables of this review have been compared between the intervention and non-intervention receiving groups of patients. In some studies the intervention is MAO and the control is OO. In the rest the intervention is an experimental factor that is being tested to find if it influences the outcome of MAO versus the control group that does not receive the intervention.

Sensitivity analyses: There has been a dearth of RCTs on MAO. It was very difficult to find the RCTs included in this review and even more difficult to find the ones that meet the inclusion criteria. There are no RCTs whose selection/non-selection for this review is dubious. Also no RCTs have been excluded from this

review which might have contributed more information except obviously the unpublished ones. Therefore sensitivety analysis is not required.

Sub-group analyses: All the meta analyses in the current review involve some and never all the selected RCTs, because all the selected RCTs are not comparable to each other.

RESULTS

Characteristics of selected RCTs
The studies included in the current systematic review are RCTs. Only some of the selected RCTs involve a direct comparison of the outcomes of surgery between MAO and OO groups of patients. The data analysis for the other studies which are different from each other is descriptive given below one by one because they cant be compared to each other as they measure different outcomes.

In all the RCTs included in this review, p-values <0.05 are regarded significant in statistics. The two groups in all studies are comparable in terms of patient characteristics (shown in the tables 4a and 4b). All the RCTs included in the review had ethical approval of the local ethical committees /boards. The results of all are valid as checked by critical appraisal tools.

Results of individual studies for outcomes (refer 4-7 to tables for abbreviations)

Ninomiya et al,2010: Statistically significant differences were found in favour of MAO with neutrophil elastase inhibitor versus MAO alone, for the duration of systemic inflammatory response syndrome-SIRS (p=.009), [median arterial oxygen pressure {P}/{F} fraction of inspired oxygen] ratio (p=.04) and interleukin8 levels (p=.04)

Biere et al, 2012:. The statistically significant differences were found in pulmonary infections (p=.005), short term quality of life and intra-operative blood loss (p<.001) in favour of MAO versus OO.

Wajed et al, 2012: {LOGIC TRIAL} The study showed that perfusion at the anastomotic site did not increase significantly by pre-operative laparoscopic ischaemic conditioning and therefore has no influence on the MAO outcome, anastomotic complications.

Shen et al, 2013: The alveolar lavage fluid interleukin levels (associated with lung inflam mation) 18 hours after MAO were significantly different {p<.046 for all inter leukin levels compared} between CV and PV groups. Oxygenation index was significantly lower in CV than in PV group (p=.046). Pulmonary complications were significantly higher in CV group than PV group(p=.021).

Cuesta et al, 2014: Statistically significant differences were found for leucocyte numbers, interleukin8 levels and prolactin levels one week post-operatively in favour of MAO versus OO with p=.004, p=.047,p=.049 respec tively. The lower levels indicate lower inflammatory response and lower immunosuppression. This accounts for fewer infections especially pulmonary infections in MAO group. The finding confirms the previously discussed Ninomiya et al study results that suppression of interleukin8 by neutrophil elastase inhibitor reduces the postoperative immunosuppression as well as SIRS as a consequence of which pulmonary complications are reduced in the MAO group.

Ito et al, 2005: showed that on day 14 there were no differences in 2 groups in vital capa city and forced expiratory volumes but peak expiratory flow was higher in MAO group than OO group [p<0.05]. Coughing ability was also better after chest physiotherapy. both of which help reduce pulmonary complications

Shen et al, 2014: found that surgery duration was longer in decubitus versus prone posit ion (p< 0.001). Blood loss was higher in DP versus PP group (p <0.001). Ergonomics of surgery were assessed.The surgeons eye blink rate and symptom scale scores were also significantly different between the two groups (p<.001) proving PP to be better than DP for thoracoscopic MAO.

Nozaki et al, 2014: Two statistically significant findings in this study were that MAO patients had fewer postoperative atelectasis (11:24 p=.041) but more risk of re-operation (10:2 p=0.016). This study involved very homogenous group of patients all with tumour stage T1bN0M0. Although registered as an RCT numbered JCOG0502 the design of this study was that of a non randomised comparison and caused patient selection bias as well as combina tion bias with the thoracoscopic MAO group more in favour of laparoscopy.

Takeuchi et al, 2015: The primary outcome weight loss 2 weeks postoperatively ,was found significantly lower in the group receiving enteral nutrition tthan the group who received par enteral nutrition (p=0.02). However it must be noted that although the patient characteris tics and intraoperative factors were comparable, the patients ability to swallow, dehydration etc. influenced the amount of feeding whether enteral or parenteral. This may have influen ced the results of this study.

Peet et al, 2015 : Statistically significant differences were found in the two patient groups for SF36 physical component (p=.003), EORTC C30 global health (p=.004) and EORTC OES18 pain (p=.001) components of quality of life (QOL) questionnares. The limitations include that only 82% questionnares were completed and trial was not powered for mid term outcomes although it was powered for short-term outcomes. Overall improvement in QOL and rate of late complications in both the groups was found to be equal .

Yamamato et al, 2016: Statistically significant differences in body temperatures were hig her in AA group versus S group at 1/2 hour post administration (p=.002), 1 hour after thor acoscopic phase of surgery (p=.008) and 2 hours after leaving the operation theatre (p<.001); Shivering score was lower in AA versus S group (p=.049). It was noted that statistically sig nificant differences were found in regards to the incidence of infectious complications of surgery (p=.029) betwee AA and S groups. The univariate analysis revealed that these infec tiouous surgical complications were related to AA administration (p=.032) and blood loss (p=.025). Multivariate analysis showed that AA administration was independently related to reduction in these infectious surgical complications (odds ratio=.301) and so was blood loss(odds ratio=.002).

Marriete et al { the French MIRO trial} study data is actually from an abstract becuse the full text is not published yet.

Results from Data extraction tables & Meta-analysis: Data synthesis The meta- analysis of data revealed the following facts:

1) Blood loss during MAO is significantly less than during OO (P<.001)

2)Post-operative pulmonary infection is significantly lower in MAO versus OO group (p<.001)

3)Postoperative hospital stay duration does not differ significantly between the two groups (p=0.745)

4)The Lymph node retreival difference between the two groups is not statistically significant.

5)Total duration of MAO operation is significantly longer than time taken for OO operation (p<.0001)
The statistical and descriptive analysis of other trials revealed the following facts:

6)Laparoscopic ischaemic conditioning does not make any significant changes in the anasto motic complications of MAO.

7)Perioperative amino acid administration reduces hypothermia, inflammatory response and immunosuppression as a consequence of which the pulmonary complications are significan- tly reduced. The infectiouous surgical complications reduce by AA administration (p=.032) and blood loss (p=.025).

8)Selective neutrophil elastase inhibitor administration during MAO leads to reduced lung injury, reduced postoperative hypoxia and reduced immunosuppression all of which lead to reduced incidence of pulmonary complications versus OO.

9)Chest physiotherapy in immediate postoperative period improves coughing ability and peak expiratory flow from day 3 postoperatively in MAO versus OO. As a consequence pulmonary complications get markedly reduced in MAO versus OO.

10)Low tidal volume controlled ventilation (CV) during MAO versus conventional tidal vol ume preserved ventilation (PV) reduces the lung injury of surgery. Oxygenation index is significantly lower in CV than in PV group (p=.046). So pulmonary complications get reduced.

11) Statistically significant differences found one week postoperatively in leucocyte numbers, inter leukin8 levels and prolactin levels favour MAO versus OO (p=.004, p=.047,p=.049 respectively).

12) MAO patients have statistically significant fewer postoperative atelectasis versus OO (p=.041) but more risk of re-operation (p=0.016).

13)Weight loss rate 2 weeks postoperatively is significantly lower with enteral nutrition versus parenteral nutrition (p=0.02) after MAO.

14)Statistically significant differences in the quality of life SF36 physical component (p=.003), EORTC C30 global health (p=.004) and EORTC OES18 pain (p=.001) components are found at 6 weeks postoperatively in MAO vs OO.

15)Surgery duration is longer in MAO in DP versus PP group (p< 0.001). Blood loss volume was higher in DP versus PP group (p <0.001).

Discussion- Summary of major findings The current systematic review and sub-group meta-analysis attempts to establish the superiority of MAO outcomes over OO outcomes and also provides evidence in regards to the ideal MAO technique plus perio-perative interven tions needed for optimising the outcomes of surgery. The aim of the review to establish level 1 evidence based on RCTs in favour of MAO for resectable OCA management has been fulfilled for one primary outcome {pu lmonary infections} and one secondary outcome {blood loss du ring surgery}. No statistically significant differences were found for the other primary outco mes - total duration of hospital stay (p=0.745) and lymph node retreival(p=1.16) between the two groups. The trials studying perioperative interventions proved that significant improve ment in the postoperative outcomes can be brought about by modifying patient position and ventilation techniques, reducing hypothermia and administering factors which reduce systemic inflammation,local lung injury, immunosuppression as a consequence of which the pulmonary complications reduce. This systematic review assessed 12 RCTs totaling 1093 pat ients. None of RCTs provided evidence for reduction in anastomotic leak rate in either group. Previous studies based on case-control/ cohort studies had indicated that anastomotic leak age might be greater in MAO group than OO but the current review established no statistically significant differences in anastomotic complications between the two groups. Also in one RCT, it has been clearly proven that gastric ischaemic conditioning does not alter anastomosis related complications. The strength of the review is that it is based on RCTs only. So the evidence generated is level 1 evidence which is considered as the best. All the RCTs included had ethical approval and provided valid results. No other systematic review on MAO outcomes based on RCTs alone has been performed till date. This review aims to provide the highest level of evidence that is available till date in favour of MAO outcomes.

An interesting result of the review was that it provided insight into periop erative modificatio ns and how they can influence MAO outcomes. If we combine the results of those trials which involved patients undergoing thoracoscopy, we can hypothesize that prone position thoraco scopy, on low tidal volume ventilation ,with administration of neutrophil elastase inhibitor and amino acids can be the ideal thoracic approach for resectable OCA when combined with immediate postoperative chest physiotherapy. All these factors indivisually lead to improved pulmonary outcomes as seen in the RCTs.

By combining the results of the trials the ideal MAO strtegy for resectable OCA patients could be derived. Thus the aim of the review is fulfilled.
Till now MAO has not replaced OO due to lack of high quality evidence and this review aimed to provide that evidence.

Limitations of the review
The limitations of the study are that

- the selected RCTs are small scale studies. -Absence of blinding in some RCTs may reduce the quality of information provided. -Minimal access technique of robotic oesophagectomy and its outcomes have not been discussed as there is no RCT currently that could have been included. -The quality of life improvement at 6 weeks was found to be statistically significant in one trial in MAO versus OO group but this parameter has not been assessed in most of the other trials.
- ICU stay could not be assessed as most of the selected trials provide no information.
- Long term survival and morbidity data is not available through any trial on MAO so far.
- The study by Peet et al included in the meta-analysis actually duplicates the short term data results of Biere et al as it is the same trial followed up for mid term outcomes at year.

Conclusions & Recommendations.
Statistically significant differences in terms of blood loss during surgery, post-operative pulmonary infection and total duration of postoperative hospital

stay, favour MAO versus OO for resectable OCA management.

The ideal MAO strategy for resectable oesophageal cancer may be thoracoscopic oesophagec tomy in prone position with low tidal volume ventilation, plus administration of amino acids with neutrophil elastase inhibitor and immediate postoperative chest physiotherapy with enteral feeding

The abdominal phase of the procedure should ideally be laparoscopy but no conclusion can be made from this study because no RCT has compared laparoscopic phase of MAO with laparotomy or robot-assisted approaches.

Randomised controlled trials involving larger patient numbers may confirm the findings in this review. The seemingly optimal strategy needs to be tested before recommending it as the gold standard of management of resectable OCA. Long term outcomes of MAO also need to be assessed through large scale RCTs .

So, the recommendations of this study are:

- confirm the findings of this review through a systematic review and meta-analysis involving large scale RCTs
- test the optimal MAO strategy found in this trial for resectable OCA management.
- long term follow up studies after MAO procedure be conducted for long term survival, mortality, morbidity and quality of life data.

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APPENDICES

Rank	Cancer	New cases diagnosed in 2012 (1,000s)	Percent of all cancers (excl. Nonmelanoma skin cancers)
1	Lung	1,825	13.0
2	Breast	1,677	11.9
3	Colorectum	1,361	9.7
4	Prostate	1,112	7.9
5	Stomach	952	6.8
6	Liver	782	5.6
7	Cervix uteri	528	3.7
8	Oesophagus	456	3.2
9	Bladder	430	3.1
10	Non-Hodgkin lymphoma	386	2.7
11	Leukaemia	352	2.5
12	Pancreas	338	2.4
13	Kidney	338	2.4
14	Uterus (endometrium)	320	2.3
15	Lip, oral cavity	300	2.1
16	Thyroid	298	2.1
17	Brain, nervous system	256	1.8
18	Ovary	239	1.7
19	Melanoma of skin	232	1.6
20	Gallbladder	178	1.3
21	Larynx	157	1.1
22	Other pharynx	142	1.0
23	Multiple myeloma	114	0.8
24	Nasopharynx	87	0.6
25	Hodgkin lymphoma	66	0.5
26	Testis	55	0.4
27	Kaposi sarcoma	44	0.3

APPENDIX 1

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. GLOBOCAN 2012 v1.1, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2014.

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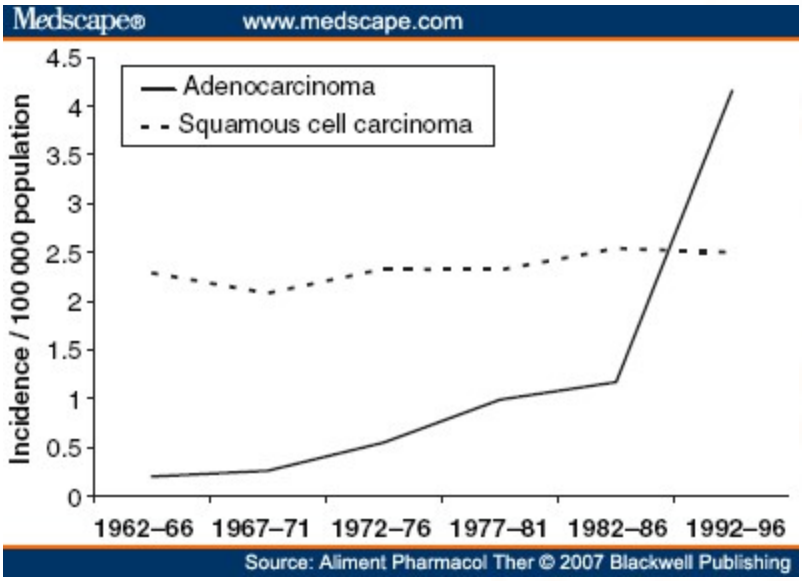
APPENDIX 2



Historical change in the male incidence of oesophageal adenocarcinoma and squamous cell carcinoma (UK data)

Available at: http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2036.2007.03325.x/full

Accessed on 16/5/2016

PPENDIX 3 ---- TNM staging of oesophageal cancer ---

Primary tumor (T)			
T1 = mucosal/submucosal involvement			
T2 = into, but not through, the muscularis propria			
T3 = through the entire wall and into the peri-luminal fat or through the serosa			
T4 = into adjacent organs (aorta, pleura, trachea, pericardium)			
Regional lymph nodes (N)			
N0 = no metastatic nodes			
N1 = regional metastatic nodes			
Distant metastasis (M)			
*Tumors of the **upper** thoracic esophagus*			
M1a	Metastasis in cervical nodes		
M1b	Other distant metastasis		
*Tumors of the **mid** thoracic esophagus*			
M1a	Not applicable		
M1b	Non-regional lymph nodes and/or other distant metastasis		
*Tumors of the **lower** thoracic esophagus*			
M1a	Metastasis in the celiac lymph nodes		
M1b	Other distant metastasis		
*Tumors of the **gastroesophageal** junction*			
M1	Distant metastasis (not celiac or gastrohepatic ligament notes)		
Esophageal cancer stage groupings [1]			
Stage	*T-stage*	*N-stage*	*M-stage*
I	Tis	N0	M0
IIA	T2–3	N0	M0
IIB	T1–2	N1	M0
III	T3	N1	M0
	T4	Any N	M0
IV	Any T	Any N	M1
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

Tis, tumor *in situ*.

Available at - http://www.gastrohep.com/ebooks/thumbnails.asp?book=1405120819&id=3

Appendix 4

Table 1: MIE outcomes in institutional series, case-control studies, and systematic reviews.

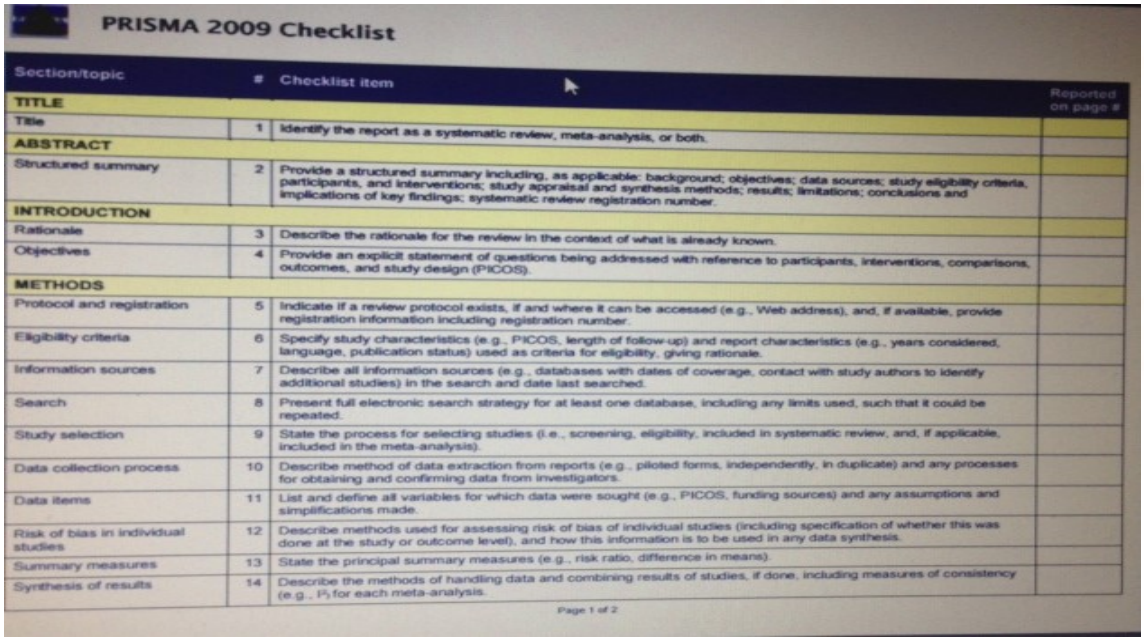
Study		Type	Leak	Pneumonia	RLN injury	Morbidity	Mortality
Institutional series							
Luketich et al. [14]	206	MIE	11.7%	7.7%	3.6%	—	1.4%
Bizekis et al. [15]	50	MIE	6%	—	—	—	6%
Rajan et al. [16]	463	MIE	—	—	—	16%	0.9%
Nguyen et al. [17]	104	MIE	9.6%	—	—	12.5%	2.9%
Ben-David et al. [18]	105	MIE	4%	9%	7%	—	1%
Ben-David et al. [19]	18	MIE	5.6%	16.7%	—	—	5.6%
Systematic reviews or meta-analyses							
Gemmill and McCulloch [20]	1398	MIE	7.7%	13.2%		46.2%	2.3%
Verhage et al. [21]	—	Open		22.9%		60.4%	3.8%
(10 case-control studies)	—	MIE		15.1%		43.8%	1.3%
Nagpal et al. [22]	612	Open	No difference				No difference
(12 case-control studies)	672	MIE	No difference				No difference

Dantoc et al. [23]	—	Open		4.4%
(17 case-control studies)	—	MIE		3%
Sgourakis et al. [24]	1008	Open versus MIE		Total complications lower with MIE
Biere et al. [25]	1061	Open versus MIE		Trends favoring MIE, but not significant
(1 randomized controlled trial and 9 case-control studies)				
Mamidanna et al. [26]	6347	Open	39.2%	4%
	1155	MIE	38 %	4.3%

MIE: minimally invasive esophagectomy.RLN: recurrent laryngeal nerve.

MIE outcomes in institutional series, case-control studies, systematic reviews ((Kim et al., 2012.) Available at-http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3419416/(Accessed on 19/09/2016)

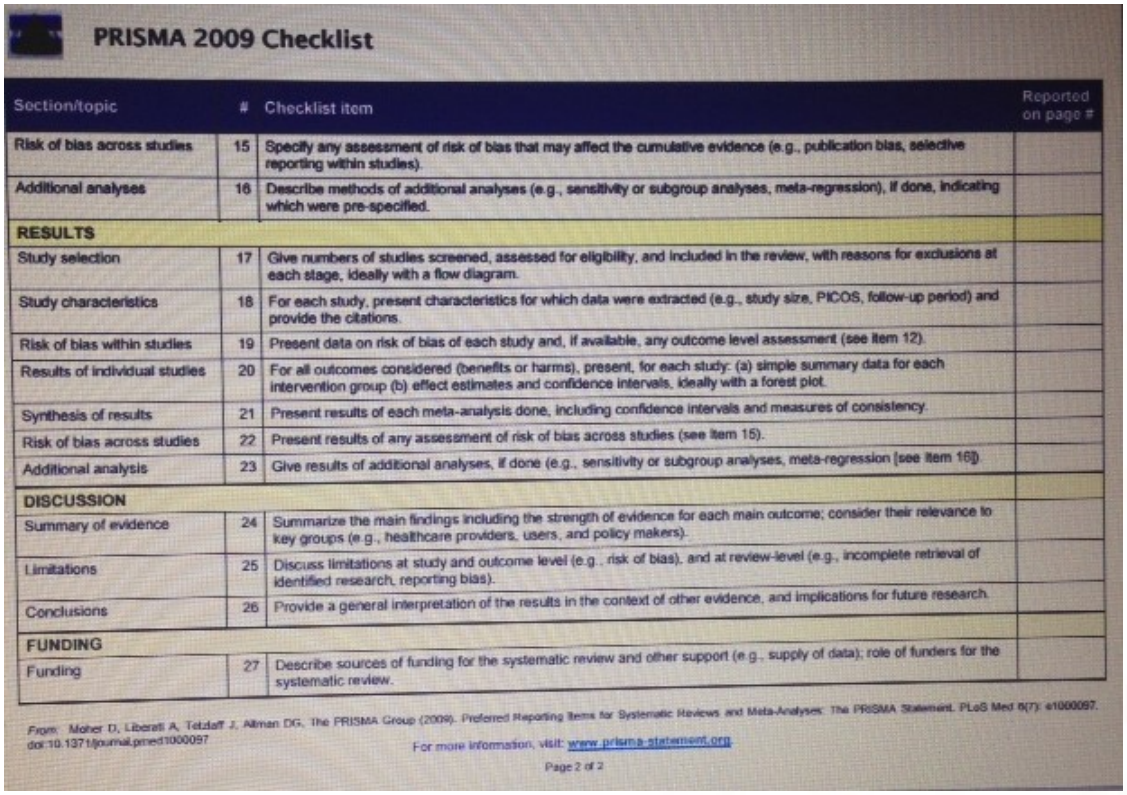
APPENDIX 5 PRISMA Checklist



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Page 1 of 2



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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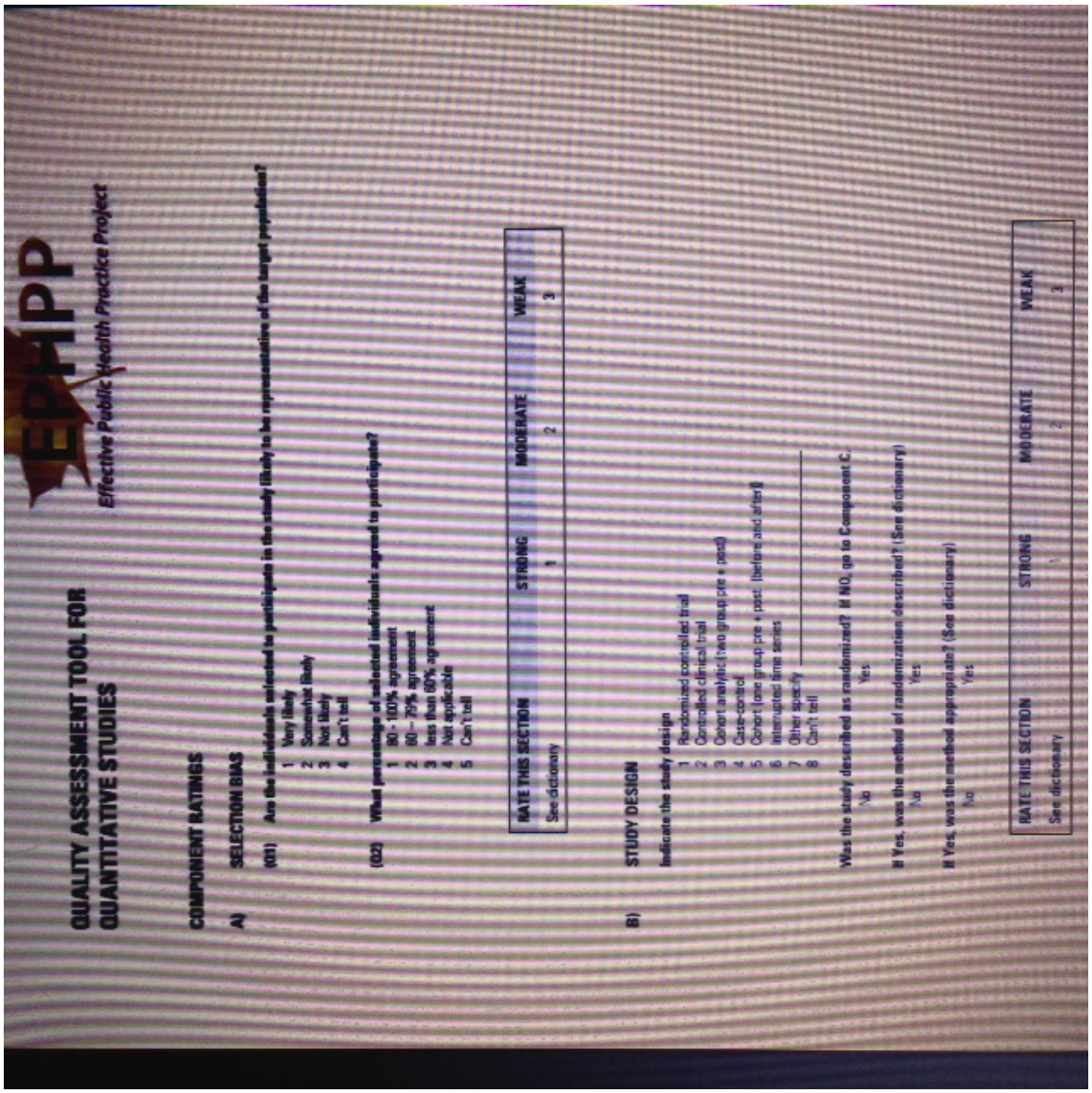
Available online at :http://prisma-statement.org/PRISMAStatement/Checklist.aspx

APPENDIX 6- EXCLUDED STUDIES AFTER FULL TEXT SEARCH

Luketich, J., Pennathur, A., Franchetti, Y., Catalano, P., Swanson, S., Sugarbaker, D., Hoyos, D., Maddaus, M., Nguyen, N., Benson, A. and Fernando, H., 2015. Minimally invasive esophagectomy: Results of a prospective phase II multicenter trial-the eastern cooperative oncology group (E2202) study. *Annals of surgery.*, 261(4), pp.702–7 Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25575253> [Accessed 14 September 2016].

APPENDIX 7

EPHPP- QUALITY APPRAISAL TOOLS



QUALITY ASSESSMENT TOOL FOR QUANTITATIVE STUDIES

EPHPP

Effective Public Health Practice Project

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) Are the individuals selected to participate in the study likely to be representative of the target population?

1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) What percentage of selected individuals agreed to participate?

1 80 - 100% agreement
2 60 - 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design

1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.
No
Yes

If Yes, was the method of randomization described? (See dictionary)
No
Yes

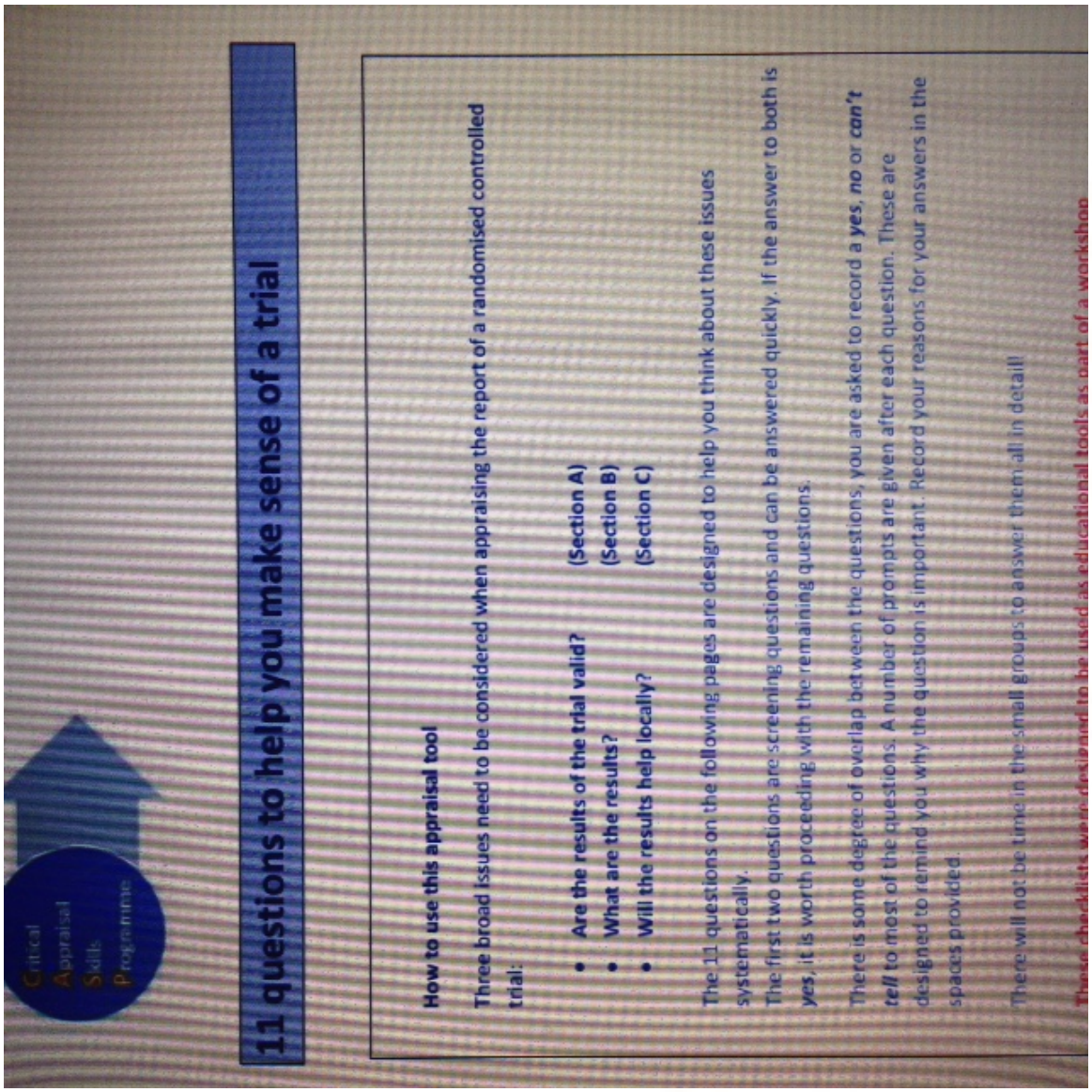
If Yes, was the method appropriate? (See dictionary)
No
Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

Available at -http://www.ephpp.ca/tools.html

Screen shots taken of the first page of the document

CASP- QUALITY APPRAISAL TOOL



Screen shots taken of the first page of the document

Available at http://www.casp-uk.net/

Appendix 8	Completed search summary for EMBASE via Pubmed

1) EMBASE; esophagectomy.ti,ab; 9890 results.
2) EMBASE; Thoracoscopic.ti,ab; 11865 results.
3) EMBASE; laparoscopic.ti,ab; 129079 results.
4) EMBASE; robotic.ti,ab; 27571 results.
5) EMBASE; "minimally invasive".ti,ab; 65598 results.
6) EMBASE; robot-associated.ti,ab; 11 results.
7) EMBASE; "robot-assisted".ti,ab; 8027 results.
8) EMBASE; "minimal access".ti,ab; 2140 results.
9) EMBASE; oesophagectomy.ti,ab; 1783 results.
10) EMBASE; 1 OR 9; 11617 results.
11) EMBASE; 2 OR 3 OR 4 OR 5 OR 6; 207159 results.
12) EMBASE; 10 AND 11; 1980 results.
13) EMBASE; 12 [Limit to: Human and (Languages English) and Publication Year 2000-2016 and (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 611 results.
14) EMBASE; 13 [Limit to: Human and (Clinical Trials Randomized Controlled Trial) and (Languages English) and Publication Year 2000-2016 and (Human Age Groups Adult 18 to 64 years or Aged 65+ years)]; 26 results.