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MASTER'S THESIS:
ESOPHAGEAL DEFECT REPAIR BY ARTIFICIAL SCAFFOLDS: A SYSTEMATIC REVIEW OF EXPERIMENTAL STUDIES AND PROPORTIONAL META- ANALYSIS

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Esophageal defect repair by artificial scaffolds: A systematic review of experimental studies and proportional meta-analysis.

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Abstract

Background: The traditional technique of gastrointestinal reconstruction of the esophagus after esophagectomy presents plenty of complications. Hence, tissue engineering has been introduced as an effective artificial alternative with potentially fewer complications. Three types of esophageal scaffolds have been used in experimental studies so far. The aim of our meta-analysis is to present the postoperative outcomes after esophageal replacement with artificial scaffolds and the investigation of possible factors that affect these outcomes.

Methods: The present proportional meta-analysis was designed using the PRISMA and AMSTAR guidelines. We searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases from inception until February 2020.

Results: Overall, thirty-two studies were included that recruited 587 animals. The pooled morbidity after esophageal scaffold implantation was 53.4% (95% CI = 36.6 to 70.0%). The pooled survival interval was 111.1 days (95% CI = 65.5 to 156.8 days). Graft stenosis (46%), post-operative dysphagia (15%) and anastomotic leak (12%) were the most common complications after esophageal scaffold implantation. Animals that underwent an implantation of an artificial scaffold in the thoracic part of their esophagus presented higher survival rates than animals that underwent scaffold implantation in the cervical or abdominal part of their esophagus ($p<0.001$ and $p=0.011$, respectively).

Conclusion: Tissue engineering seems to offer an effective alternative for the repair of esophageal defects in animal models. Nevertheless, issues like graft stenosis and lack of motility of the esophageal scaffolds need to be addressed in future experimental studies before scaffolds can be tested in human trials.

Author contribution:

Dimitrios Schizas: data collection, writing.

Maximos Frountzas: data analysis, writing.

Emmanouil Sgouromallis: data collection, writing.

Eleftherios Spartalis: data analysis.

Konstantinos S. Mylonas: study design.

Theodore G. Papaioannou: study design.

Dimitrios Dimitroulis: study design.

Nikolaos Nikiteas: evaluation of meta-analysis and remarks during wriring.

Introduction

Esophagectomy, which usually includes a wide local excision and lymphadenectomy, remains the treatment of choice for esophageal malignancy, the incidence of which has presented a marked increase over the past three decades (1, 2). Except from the cases, that neither gastric nor colonic conduits are available for esophageal reconstruction, the use of gastrointestinal segments to close the gap after esophagectomy has been the gold standard approach so far, despite post-operative complications that could lead to high morbidity and mortality (3). The most common post-operative complications are anastomotic leakage, strictures, mediastinitis, diarrhea, dumping-like symptoms and reflux problems (4). Therefore, tissue engineering and regenerative medicine have been utilized to create artificial grafts that could be used as the basis for esophageal regeneration (5).

Tissue engineering could be defined as the application of biological, chemical and physical methods, that follow technical principles related to design, research, purchasing and control, leading to the construction of a biocompatible complex dedicated to the repair, restoration or regeneration of living tissue through the utilization of biomaterials, cells and/or factors (6, 7). The most crucial step for the successful appliance of tissue engineering in esophagus is the scaffold that would be utilized as a graft. A scaffold is a natural or synthetic complex that is biocompatible with cells. Its morphology, geometry, thickness and porosity (pore size) are known to affect cell adhesion, proliferation, tissue organization, angiogenesis and the formation of the ECM (extracellular matrix) (8).

Three approaches of scaffold-based esophageal tissue engineering have presented the most promising results until now, mainly in experimental studies. The first development was related to non-absorbable constructs, based on silicone and

collagen. However, the need to remove the silicone tube using endoscopy was the main disadvantage of this material (9). In addition, polymeric absorbable scaffolds have been used since the 1990s. The main polymeric material used was poly (glycolic) acid combined with collagen. Nevertheless, the problem of stenosis remained prevalent in most studies using an absorbable construct (10). Finally, decellularized scaffolds have been used since 2000. The potential of this new approach has not been fulfilled to date. Indeed, stenosis occurs when the esophageal defect is circumferential, regardless of the scaffold materials (11). On the other hand, cell supplementation could decrease the rate of stenosis, whereas the type of cells and their roles have not been yet defined (12).

The aim of the present meta-analysis is to present the outcomes and the post-operative complications of all the available experimental studies that utilized a tissue-engineered scaffold in order to close a circumferential esophageal defect. Moreover, the present meta-analysis investigates any possible relationship between the animal species, the part of esophagus that was replaced and the type of scaffold that was used, and the post-operative outcomes after esophageal scaffold implantation.

Materials and methods

The present study was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and AMSTAR (A MeaSurement Tool to Assess systematic Reviews) guidelines (13, 14).

Information sources and search methods

We searched Medline, Scopus, Clinicaltrials.gov, EMBASE, Cochrane Central Register of Controlled Trials CENTRAL and Google Scholar databases. The date of our last search was June 5th, 2020. “Snow-balling” was also performed by searching the

references of articles that were retrieved in full text to minimize the possibility of article losses. The main search algorithm that was applied was the following: (esophageal[All Fields] AND scaffold[All Fields] AND ("tissue engineering"[MeSH Terms] OR ("tissue"[All Fields] AND "engineering"[All Fields]) OR "tissue engineering"[All Fields]). The stages of article selection are depicted in the PRISMA flow diagram (Figure 1).

The studies were selected in three consecutive stages. Firstly, after checking for duplicate publications, the titles and abstracts of all electronic articles were screened to evaluate their eligibility. Secondly, the articles that were presumed to meet the criteria were retrieved as full texts. In the third stage, we selected all observational studies (both prospective and retrospective) that met the inclusion criteria. Two authors performed the electronic search of articles and tabulated data on duplicated pre-structured forms. The data were then reviewed by all authors and all conflicts were resolved by the consensus of all authors.

Types of studies

No language or date restrictions were applied during the literature search. All articles that were written in Latin alphabet were considered as potentially eligible for inclusion. In addition, articles written in other languages were considered eligible, when they could be translated in plain English text using the Google Translate service. All experimental animal studies that presented the outcomes after repairing circumferential esophageal defects by artificial esophageal scaffolds were included in our study. A partial repair of the esophageal wall, such as the coverage of a myomectomy site with a scaffold, was not considered as part of the inclusion criteria. In addition, experimental studies that assessed esophageal scaffold growing in animals by implanting them in different anatomical sites from esophagus, such as peritoneal cavity, were not included.

Observational human studies, case reports and reviews were not included in the present meta-analysis as well.

Investigated outcomes

The primary outcome of the present meta-analysis was the overall morbidity rate after repair of esophageal defects using artificial scaffolds in animals. The mean survival interval and the rates of different complications after esophageal scaffolds utilization for repairing esophageal defects in animals were predefined as secondary outcomes.

Quality assessment

The methodological quality of the included studies was assessed with the SYRCLE's risk of bias tool, which has been adjusted for aspects of bias that play a specific role in animal intervention studies (15). It contains 10 entries that are related to selection bias, performance bias, detection bias, attrition bias, reporting bias and other biases. Signaling questions are included to help judge risk of bias, and the possible answers are "low", "high" or "unclear". At the end, a summary of the number of studies that had a low, a high, or an unclear risk of bias or concerns about applicability for each entry is formed, represented by a different color (Figure 2).

Statistical analysis

The proportional meta-analysis was conducted using the MedCalc Statistical Software version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018) for the pooled overall morbidity and the Open-Meta Analyst statistical software for the pooled survival interval (16). Confidence intervals were set at 95%. The overall morbidity rate and survival interval were calculated as proportions and 95% CIs for each study, and then data was pooled to derive pooled proportions and 95% CIs. A random-effects model (DerSimonian-Laird) using arcsine

square root (Freeman-Tukey) transformation was implemented to calculate pooled estimates of proportions as the back-transform of the weighted mean of the transformed proportions, along with the 95% CI, as methodological heterogeneity was expected to be high among the included studies (17). A quantitative analysis for the secondary outcomes was not allowed, due to the great asymmetry of the data provided by the included studies. The inconsistency index (I^2) was used as a measure of inter-study heterogeneity (18). High heterogeneity was confirmed with a significance level of $p< 0.05$ and I^2 value of $\geq 50\%$.

Univariate meta-regression analysis was performed with Open Meta- Analyst statistical package. Four covariates were defined for the comparison of survival interval and overall morbidity between studies that used animals of different species: “pigs”, “dogs”, “rabbits” and “rats”, depending on the animal species that each study utilized. In addition, survival interval and overall morbidity were compared between studies that utilized different types of scaffolds by using three covariates: “non-absorbable”, “absorbable” and “uncellularized”, according to the type of scaffold that each study utilized. Finally, the impact of the esophageal part, that was replaced in every study, on overall morbidity and survival interval was evaluated by determining three covariates: “thoracic”, “cervical” and “abdominal”, according to the esophageal part that had been replaced in each study.

Protocol registration

This study was registered with the Open Science Framework (http://www.osf.io/) and its unique identifying number was: 10.17605/OSF.IO/CVFE6.

Results

Excluded studies

Twelve studies were excluded from the meta-analysis. Four studies described the implantation of esophageal scaffolds in anatomical sites other than the esophagus, such as the abdominal wall, the omentum and the subcutaneous tissue of the animals (19-22). Five studies referred to the segmental replacement of the esophageal wall by esophageal scaffolds; for instance, implantation of esophageal scaffolds in the mucosa or submucosa, even in the muscular layer of esophageal wall, after surgical or endoscopic resection of these layers in the animals (23-27). Two studies presented the *in vitro* development of an esophageal scaffold that had been produced by esophageal mesenchymal stem cells of animals (28, 29). Finally, the rest studies were related to the enhancement of esophageal anastomoses by scaffolds, the neuron cell growing after esophageal scaffolds implantation in animal models, whereas in a study clinical outcomes after esophageal scaffolds utilization were not provided (30-32).

Included studies

Thirty-two studies were included in the meta-analysis that involved 587 animals of different species which underwent esophageal defect repair by using artificial scaffolds (33-64). Among these animals, 325 complications were reported.

Data tabulation

Data on variables of interest were tabulated in three structured forms. Table 1 briefly presents the characteristics of each study, including the animal species that each study utilized, the part of the esophagus that was replaced by esophageal scaffolds and the follow-up period of the animals. In addition, it summarizes the characteristics of the esophageal scaffolds that were used in each study, including the graft type, the size of the patch and whether the scaffold was seeded with cells or not. Table 2 refers to the

clinical outcomes after tissue engineered scaffold repair of esophageal defects in the animals of each study, including any possible complication that was reported, such as stenosis of the graft, leak at the site of anastomosis, abscess formation, esophageal fistula, ulceration of the graft, post-operative dysphagia, esophageal diverticula, complete obstruction of the graft, dislocation of the graft and pneumonia. Table 2 demonstrates the overall morbidity rate and the survival interval of the animals for the studies that were available.

Primary outcome

The overall morbidity rate of artificial scaffolds utilization for esophageal defect repair ranged from 0% to 100% and the net pool rate after proportional meta-analysis (random effect) was 53.4% (95% CI = 36.6 to 70.0%). The proportion meta-analysis plot of morbidity rate is depicted in Figure 3. There was marked statistical heterogeneity (I^2 = 98.94%).

Secondary outcomes

The survival interval for the animals that underwent implantation of an esophageal scaffold ranged from 5 to 736 days and the net pool survival after proportional meta-analysis (random effect) was 111.1 days (95% CI = 65.5 to 156.8 days). The proportional meta-analysis plot of the survival interval is shown in Figure 4. There was marked statistical heterogeneity (I^2 = 99.99%).

Overall, 325 complications were reported after the implantation of esophageal scaffolds in 587 animals. The most common complication was graft stenosis with 151 animals presenting with this complication (46%). In addition, 40 (12%) animals demonstrated an anastomotic leak after esophageal scaffold utilization, 6 (2%) animals had a post-operative abscess formation, 8 (2%) animals presented an esophageal fistula and in 4 (1%) animals a graft ulceration was found after endoscopic examination.

Moreover, 49 (15%) animals had post-operative dysphagia, 10 (3%) animals presented esophageal diverticula, 15 (5%) demonstrated a complete graft obstruction, in 20 (6%) animals a dislocation of the graft was reported and in 22 (7%) animals the diagnosis of post-operative pneumonia was made.

Sensitivity analysis

Meta-regression analysis demonstrated that animals with implantation of an artificial scaffold in the thoracic part of their esophagus ("thoracic" group) had superior survival (181 days, range 126-236 days) than animals that underwent implantation of an artificial scaffold in the cervical ("cervical" group) (57 days, range 49-65 days) or abdominal ("abdominal" group) (67 days, range 36-99 days) part of their esophagus ($p<0.001$ and $p=0.011$, respectively).

On the other hand, no statistically significant difference was observed in survival of animals between studies that utilized different animal species ("dogs", "pigs", "rats" or "rabbits") ($p=0.255$). In addition, no difference was outlined in overall morbidity between studies depending on the animal species ("dogs", "pigs", "rats" or "rabbits") that were utilized ($p=0.052$).

Moreover, no statistically significant difference was demonstrated in survival of animals between studies that used different types of scaffolds ("non-absorbable", "absorbable", "decellularized") ($p=0.062$). Finally, no difference was highlighted in overall morbidity between studies depending on the type of scaffold ("non-absorbable", "absorbable", "decellularized") that was used ($p=0.44$).

Quality assessment

According to the SYRCLE's risk of bias tool for experimental studies, all the studies presented an unclear risk for selection bias. In addition, the majority of the

studies (around 80%) presented an unclear risk for performance bias. The possibility of detection bias was mixed, as 90% of the included studies provided a random outcome assessment, while in 35% of the studies a blinded outcome assessment was not provided. Finally, there was a low risk of attrition, reporting and other types of bias in almost all the included studies (Figure 2).

Discussion

Main findings

Our meta-analysis demonstrated a remarkable survival interval for animals that underwent esophageal defect repair by artificial scaffolds in experimental studies. However, over half of the animals that underwent such esophageal scaffold implantations presented with at least one post-operative complication. The most common complication was graft stenosis, followed by post-operative dysphagia and anastomotic leakage. Less common complications such as abscess formation, esophageal fistula, graft ulceration, esophageal diverticula, scaffold obstruction, graft dislocation and pneumonia were also reported. Furthermore, animals that underwent an implantation of an artificial scaffold in the thoracic part of their esophagus had higher survival rates than animals that underwent scaffold implantation in the cervical or abdominal part of their esophagus, whereas there was no correlation between the overall morbidity and the animal species that each study utilized, the esophageal part of the scaffold implantation or the type of scaffold that was used.

Literature update

Similarly to our study's findings, graft stenosis still remains the greatest problem of the artificial scaffolds that have been used so far for the repair of an esophageal defect, as reported in the literature (65). However, lack of motility, and therefore

decreased functionality, as a result of no innervation has been also reported in the literature as a very crucial disadvantage for the artificial scaffolds that have been used so far for the repair of esophageal defects (66). The "hybrid construct", which is an artificial combination of decellularized matrices and mesenchymal stem cells, seems to be the ideal experimental model that has been described so far (67). On the one hand, this model is based on the cell adhesive and molecular supportive properties of extracellular matrix (ECM), that are provided by the scaffolds that are manufactured by decellularized matrices (68). On the other hand, the pluripotency of mesenchymal stem cells that could differentiate in different cell types, such as muscular, epithelial or nerve cells, in the suitable molecular environment gives to this model the advantage of providing a completely functional scaffold for esophageal replacement (69, 70). Finally, except from experimental studies, artificial esophageal scaffolds have been tested in only a few human cases, mainly for the prevention of esophageal stricture after partial endoscopic mucosal excisions, with promising results (71).

Strengths and weaknesses of our study

To our knowledge, the present meta-analysis is the first in the international literature that systematically presented all the available experimental studies that are related to the outcomes after esophageal defect repair using artificial scaffolds, based on a meticulous review of a wide range of databases. The search strategy was not restricted by language and date criteria; hence, limiting the possibility of potential article losses that could significantly alter our findings. Nonetheless, the systematic nature of the present study required that all studies that met the inclusion criteria should be part of it; therefore, a great heterogeneity was observed among included studies in the terms of animal species, replaced esophageal parts, types and lengths of grafts. When it was possible, the effect of these parameters on our primary outcomes was

investigated. Moreover, the difference in surgical technique among different animal species could not be interpreted, although there was no difference regarding the morbidity rate and the overall survival after scaffold transplantation between the different animal species. Furthermore, the potential effect of primary feeding through a gastrostomy on complications after scaffold transplantation was not demonstrated in the included studies. In addition, due to the small number of animals in the included experimental studies our conclusions should be interpreted with caution. Moreover, the absence of control groups in the included studies did not allow a comparative analysis between the different types of esophageal scaffolds. Finally, the small number and the high level of heterogeneity of studies that presented the outcomes after implantation of scaffolds based on decellularized matrices that were seeded with stem cells, did not allow inclusion of seeding with stem cells as a factor in a meta-regression analysis.

Implications for future research

Tissue engineering seems to be an effective alternative for closing esophageal gaps after esophagostomy (72). Nevertheless, there are some issues that need to be addressed in order for these alternatives to get approval for clinical trials. First of all, graft stenosis and lack of motility still remain two major problems of the available esophageal scaffolds that decrease their functionality and effectiveness. The potential role of mesenchymal stem cells seems to be the key in facing these two problems, as their pluripotency offers a wide spectrum of cell differentiation towards the direction of muscular, epithelial or nerve cells, that could offer motility, while the esophageal lumen diameter would be preserved (72). Future molecular studies should demonstrate the molecular pathways through which the ECM and mesenchymal stem cells interact in order to guide their differentiation towards the desired cell lines (muscular, nerve). In addition, the role of neovascularization after an esophageal scaffold transplantation

should be investigated, as the new vessels might provide the appropriate protection against saliva and bacteria form the oral cavity. Moreover, a comparison between the esophageal scaffolds that are manufactured by decellularized matrices that have been seeded and not seeded with cells, in terms of effectiveness and morbidity, would be extremely useful in future experimental studies.

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Tables and figures

Table 1. Animal and Scaffold characteristics							
Year; author	***Animal No***	***Animal Model***	***Part of Esophagus***	***Size of Patch***	***Graft Type***	***Cell Seed***	***Follow-Up (days)***
1983; Kawamura	14	Dogs	Thoracic	3,5,7 or 10 cm circumferential	Collagen - silicone copolymer	NO	212
1983; Fukushima	16	Dogs	Thoracic	5-6 cm circumferential	Phycron tube (silicone rubber) covered with Dacron mesh	NO	2580
1993; Natsume	19	Dogs	Cervical	5cm circumferential	Collagen sponge - silicone tube double layered	NO	370
1994; Takimoto	29	Dogs	Cervical	5cm circumferential	Collagen sponge - silicone tube double layered	NO	801
1998; Takimoto	43	Dogs	Cervical	5cm circumferential	Collagen sponge - silicone tube double layered	NO	360
1999; Yamamoto	9	Beagle dogs	Thoracic	5cm	Collagen sponge with a double layered silicone tube	NO	540
2000; Badylak	15	Mongrel dogs	Cervical2	Semi-circumferential or 5-6 cm circumferential	Extracellular Matrix derived from SIS or UBS	NO	450
2000; Saito	12	Rabbits	Cervical	2cm circumferential	Artificial dermis (collagen sponge and silicone), split thickness skin and latissimus dorsi muscle	NO	16
2000; Yamamoto	14	Beagle dogs	Thoracic	5cm circumferential	Collagen sponge - silicone tube double layered with or without omental pedicle wrapping	NO	1080
2001; Isch	12	Dogs	Cervical	2 x 1 cm	Alloderm	NO	90
2004; Lynen Jansen	10	Chinchilla rabbits	Abdominal	0.5 x 1 cm	PGL mesh vs PVDF mesh	NO	84
2005; Badylak	22	Dogs	Cervical	5cm circumferential	ECM bioscaffold derived from porcine urinary bladder	NO	230
2006; Lopes	67	Lewis rats	Cervical (34) + Abdominal (33)	10mm semi-circumferential	Porcine SIS	NO	150
2006; Urita	27	F344 rats	Abdominal	3-4x5 mm (semi-circumferential)	Gastric acellular matrix	NO	540
2008; Juhasz	12	Beagle dogs	Cervical	6cm circumferential	Cryopreserver tracheal allograft (for 21 days at -86 ºC)	NO	56
2008; Nakase	12	Beagle dogs	Thoracic	3cm circumferential	PGA with smooth muscle seeded with oral keratinocytes and fibroblasts vs no seeding	BOTH	490
2009; Doede	14	Piglets	Cervical	3-4 cm circumferential	SIS porcine	NO	31
2009; Liang	20	Pigs	Thoracic	7cm circumferential	Nitinol composite artificial esophagus with polyester connecting rings versus without rings	NO	180
2012; Liang	10	Pigs	Thoracic	6cm circumferential	Nitinol composite artificial esophagus with polyester connecting rings with FRM applied versus without FRM	NO	180
2013; Tan	12	Beagle dogs	Cervical2	5 x 2.5cm (semi-circumferential)	SIS vs SIS seeded with bone marrow MSCs	BOTH	84
2014; Chung	11	Sprague-Dawley rats	Cervical	N/A	3 layered hybrid prostheses (inner PCL, middle SF, outer PCL layer)	NO	14
2014; Diemer	20	New Zealand white rabbits	Abdominal	0.6 x 1 cm	Poly-ε-caprolactone mesh	NO	30
2014; Jiang	13	Beagle dogs	Cervical	2cm circumferential	Artificial esophagus made of non-degradable polyurethane materials	NO	360
2015; Algarrahi	62	Sprague-Dawley rats	Abdominal	7 x 3 mm	Bi-layer silk fibroin scaffold vs SIS	NO	60
2015; Liang	20	Pigs	Thoracic	2cm circumferential	Nitinol composite artificial esophagus with polyester connecting rings	NO	360
2015; Poghosyan	18	Minipigs	Cervical	5cm circumferential	Acellular matrix (SIS) seeded with autologous skeletal myoblasts, covered by a human amniotic membrane seeded with autologous oral epithelial cells	BOTH	360
2016; Park	6	New Zealand	Cervical	10 x 5 mm	3D printed polycaprolactone scaffold coated with MSCs seeded in fibrin or not coated	BOTH	21

		white rabbits					
2017; Catry	20	Gottingen mini pigs	Abdominal	3cm circumferential	Acellular matrix seeded with autologous MSCs versus acellular matrix without seeding	BOTH	119
2017; Okuyama	4	Beagle dogs	Cervical	10 x 20 mm	Biosheet	NO	84
2018; Chung	10	Sprague-Dawley rats	Cervical	N/A	Omentum cultured oesophageal scaffold reinforced by a 3D-printed ring	NO	15
2018; La Francesca	8	Yucatan mini pigs	Thoracic	6cm circumferential	Electrospun polyurethane scaffold seeded with autologous adipose derived MSCs	YES	570
2018; Luc	6	Pigs	Abdominal	5cm circumferential	Decellularized matrix with or without omental maturation	NO	35

Table 1. The characteristics of the esophageal scaffolds and the animal models that were used in the included studies for the esophageal defects repair. SIS, small intestinal submucosa; UBS, urinary bladder submucosa; PGL, polyglactin; PVDF, polyvinylidene fluoride; ECM, extracellular matrix; PGA, polyglycolic acid; FRM, feeding regulation measures; MSCs, mesenchymal stem cells; PCL, poly(ε-caprolactone); SF, silk fibroin N/A, data were not available.

Table 2. Clinical Outcomes												
Year; author	***Steno-sis***	***Leak***	***Absces s***	***Fistu -la***	***Ulcerati-on***	***Dysppha gia***	***Diverti cula***	***Graft Obstru-ction***	***Dislo-cation***	***Pneu-monia***	***Survival (days)***	***Overall Morbidit y***
1983; Kawamura	3/14	5/14	N/A	1/14	N/A	4/14	N/A	N/A	N/A	N/A	39 ± 29	100%
1983; Fukushima	7/16	5/16	N/A	1/16	N/A	1/16	N/A	N/A	N/A	2/16	736 ± 498	88%
1993; Natsume	7/19	0/19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	41 ± 35	24%
1994; Takimoto	18/29	0/29	N/A	N/A	N/A	N/A	N/A	N/A	N/A	8/29	207 ± 96	72%
1998; Takimoto	22/43	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	93 ± 35	51%
1999; Yamamoto	1/9	0/9	N/A	N/A	N/A	1/9	N/A	N/A	0/9	N/A	N/A	11%
2000; Badylak	4/15	N/A	N/A	N/A	N/A	4/15	N/A	N/A	N/A	N/A	125 ± 63	27%
2000; Saito	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9/12	5 ± 2	100%
2000; Yamamoto	13/14	1/14	N/A	N/A	N/A	2/14	N/A	N/A	N/A	N/A	240 ± 154	43%
2001; Isch	0/12	0/12	N/A	N/A	N/A	0/12	0/12	N/A	N/A	N/A	60 ± 14	17%
2004; Lynen Jansen	0/10	3/10	1/10	N/A	N/A	N/A	N/A	N/A	1/10	1/10	N/A	60%
2005; Badylak	12/22	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	73 ± 28	55%
2006; Lopes	0/67	0/67	N/A	N/A	N/A	0/67	N/A	2/67	N/A	N/A	N/A	6%
2006; Urita	0/27	3/27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	128 ± 63	11%
2008; Juhasz	N/A	0/12	N/A	N/A	N/A	0/12	N/A	N/A	N/A	N/A	42 ± 6	17%
2008; Nakase	8/12	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/12	99 ± 75	67%
2009; Doede	13/14	2/14	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	20 ± 2	93%
2009; Liang	10/20	3/20	N/A	N/A	N/A	N/A	N/A	1/20	1/20	N/A	178 ± 69	75%
2012; Liang	N/A	0/10	N/A	N/A	N/A	5/10	N/A	N/A	5/10	N/A	180 ± 0.05	50%
2013; Tan	0/12	0/12	N/A	0/12	N/A	0/12	0/12	N/A	N/A	N/A	56 ± 16	0%
2014; Chung	N/A	N/A	0/11	3/11	N/A	N/A	N/A	2/11	N/A	N/A	N/A	45%
2014; Diemer	2/20	1/20	1/20	N/A	N/A	N/A	10/20	N/A	1/20	1/20	N/A	80%
2014; Jiang	N/A	9/13	N/A	N/A	N/A	12/13	N/A	N/A	12/13	N/A	130 ± 60	77%
2015; Algarrahi	N/A	1/62	1/62	0/62	N/A	0/62	0/62	N/A	N/A	N/A	N/A	8%
2015; Liang	N/A	0/20	N/A	N/A	N/A	20/20	N/A	N/A	N/A	N/A	258 ± 53	100%
2015; Poghosyan	10/18	5/20	N/A	N/A	3/18	N/A	N/A	N/A	N/A	N/A	108 ± 51	100%
2016; Park	0/6	0/6	N/A	N/A	N/A	N/A	N/A	0/6	N/A	N/A	21 ± 1.0	0%

2017; Catry	19/20	0/20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	54 ± 12	100%
2017; Okuyama	0/4	0/4	N/A	N/A	N/A	0/4	N/A	N/A	N/A	N/A	56 ± 27	0%
2018; Chung	N/A	0/10	0/10	0/10	N/A	N/A	N/A	10/10	N/A	N/A	N/A	100%
2018; La Francesca	N/A	0/8	N/A	1/8	1/8	N/A	N/A	N/A	N/A	N/A	169 ± 155	25%
2018; Luc	2/6	2/6	3/6	2/6	N/A	N/A	N/A	N/A	N/A	1/6	29 ± 10	83.3%
TOTAL	***151 (46%)***	***40 (12%)***	***6 (2%)***	***8 (2%)***	***4 (1%)***	***49 (15%)***	***10 (3%)***	***15 (5%)***	***20 (6%)***	***22 (7%)***		

Table 2. The clinical outcomes after esophageal scaffold implantation. Data are mean ± SD or median (range) unless otherwise specified. N/A, data were not available.

Figure legends

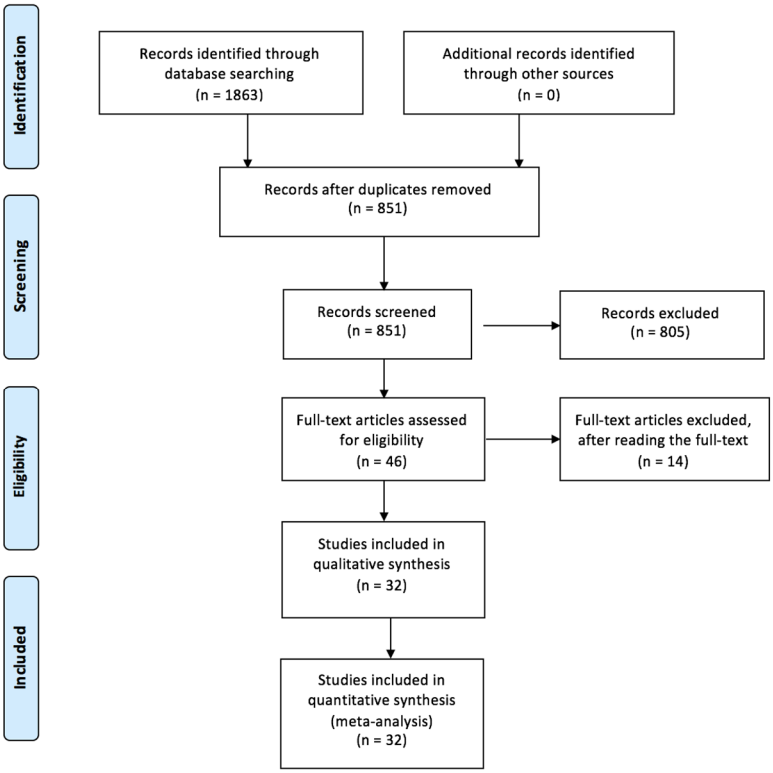

Figure 1. The PRISMA flow chart of study selection.

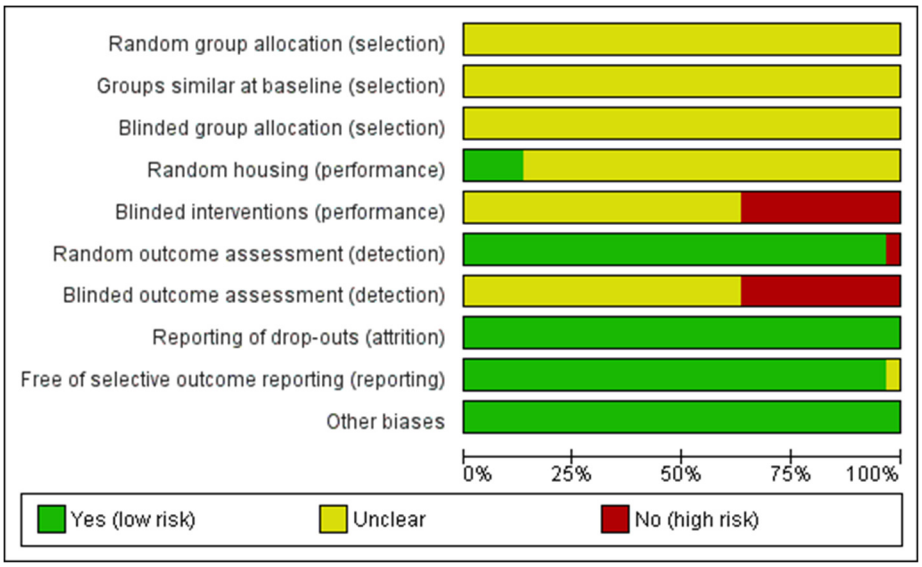

Figure 2. The methodological assessment of the included studies according to the SYRCLE's risk of bias tool for experimental studies.

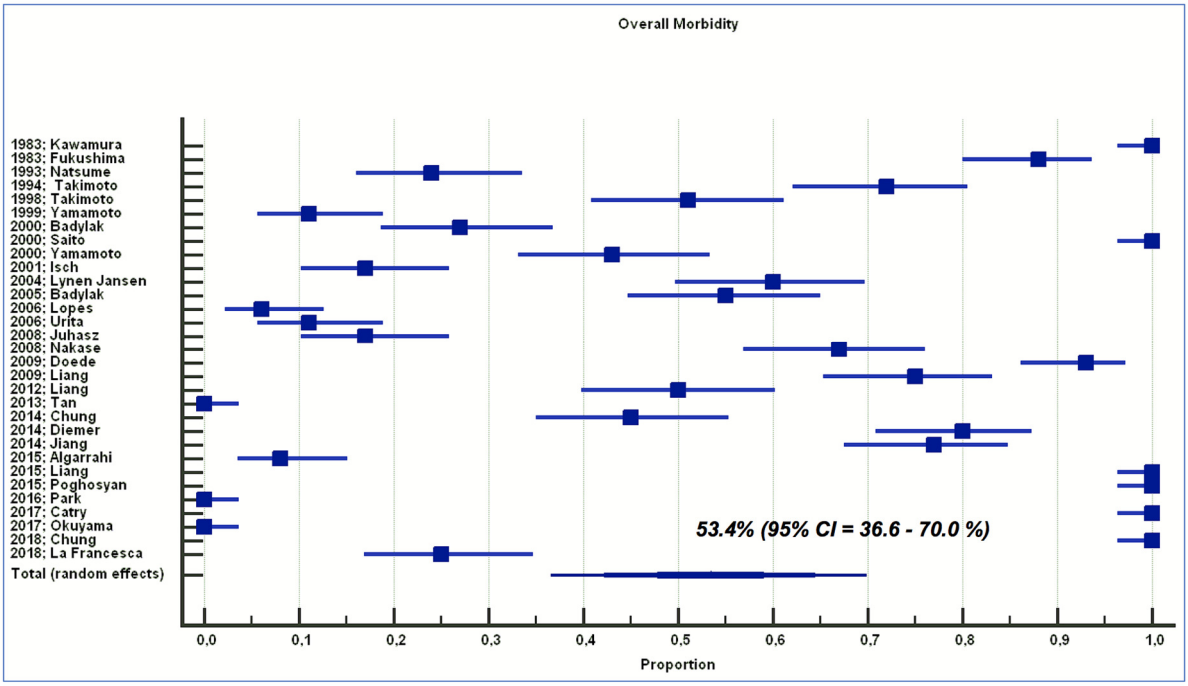

Figure 3. The proportion meta-analysis plot of all the studies showing the net morbidity rate of 53.4% (95% CI = 36.6 to 70.0). (Squares, proportions; Diamond, pooled proportions for all studies; Horizontal lines, 95% CI)

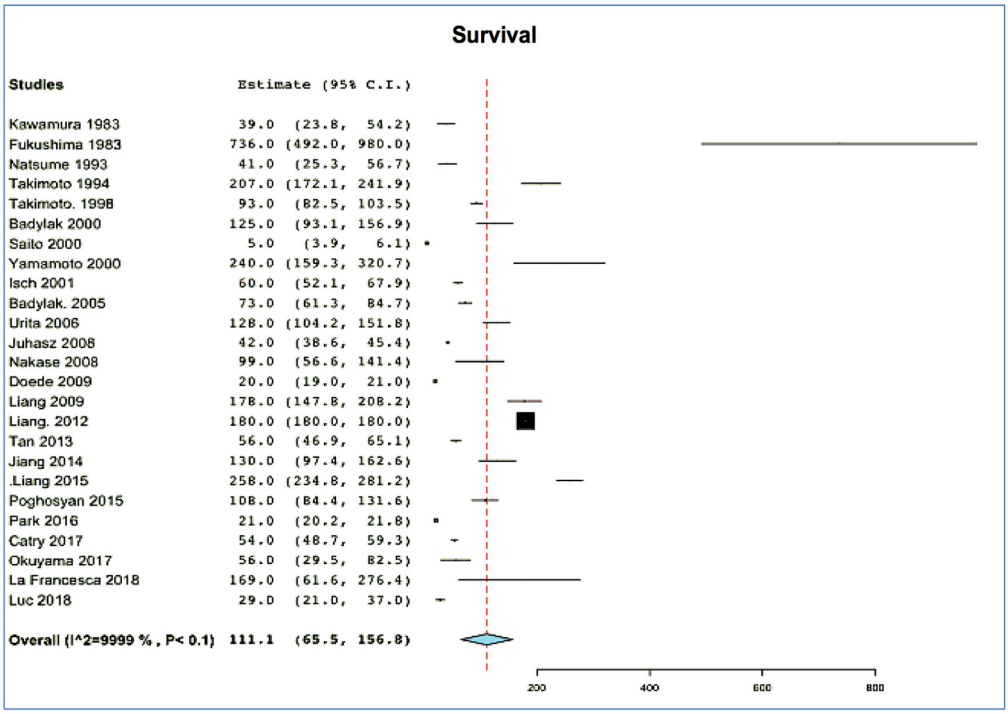

Figure 4. The proportion meta-analysis plot of all the studies showing the net survival interval of 111.1 days (95% CI = 65.5 to 156.8 days). (Squares, proportions; Diamond, pooled proportions for all studies; Horizontal lines, 95% CI)