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New approaches in esophageal carcinomas

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Abstract: New approaches in the treatment of esophageal cancer comprise endoscopy with refinements of esophagoscopic intraluminal resection by endoscopic submucosal dissection. Radical open surgery is more and more replaced by minimally invasive esophagectomy (MIO), especially in the hybrid technique with laparoscopic gastrolysis and transthoracic esophageal resection and gastric pull-up. Total MIO also in the robotic technique has not yet shown that it produces superior results than the hybrid technique. Fluorescent dye can improve the intraoperative visualization of the vascularization of the gastric conduit. The individualization of neoadjuvant therapy is the magic word in clinical research of multimodal treatment of esophageal cancer. This means response prediction based on molecular markers or clinical response evaluation. The documentation of the diversity of postoperative complications is now standardized by an international consensus. The value of enhanced recovery after surgery is not yet approved compared to conventional management.

Keywords: adenocarcinoma; enhanced recovery after surgery; esophageal cancer; neoadjuvant therapy; postoperative complications; squamous cell carcinoma.

Introduction

New approaches in esophageal cancer are, on the one hand, technical concerning endoscopic intraluminal therapy or minimally invasive esophagectomy (MIO) and the visualization of vascularization of the gastric conduit. On the other hand, new insights into the genomic causes for the malignant degeneration of Barrett's esophagus open the possibility for more effective and individualized endoscopic surveillance. Individualized multimodal treatment is tried to be based on response prediction or on the clinical evaluation of response. The standardization of documentation of complications after esophagectomy is a new achievement because the comparability of data is poor. Finally, enhanced recovery after surgery (ERAS) is a topical issue that is tried to establish in centers for esophageal surgery.

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Current guidelines for the treatment of esophageal cancer

For the description of new therapeutic approaches in solid tumors, it is necessary to describe the current standards that are the basis of new developments. The German S3 guideline for esophageal cancer defines the current standard that was completed and published in 2015 [1, 2]. The algorithms for the treatment of adenocarcinoma (AC) or squamous cell carcinoma (SCC) in patients functionally fit for surgery are shown in Figures 1 and 2. The diagnostics with endoscopy, biopsy, endosonography, and spiral computed tomography (CT) scan are established and lead to a clinical TNM staging.

cT1

In T1 category, mucosal (T1a) carcinomas can be removed by endoscopic means, preferably endoscopic submucosal dissection (ESD), if a resection without residual tumor (R0) is achievable [3, 4]. On the contrary, submucosal infiltration (T1b) affords radical surgical resection because the risk of lymph node metastasis is too high [5]. Only in deep mucosal infiltration (m3) of an SCC that primary surgery is recommended. New approaches of intraluminal endoscopic resection are aiming on superficially infiltrating (sm1) submucosal carcinomas that have a low risk of lymphatic metastasis [5]. These characteristics are ≤ 2 cm diameter, no ulceration, L0, and V0. However, outcome data on the prerequisites derive, except for one study, only from Asian populations and are difficult to compare to European patients [6, 7]. New endoscopic approaches with intraluminal circumferential resections to remove

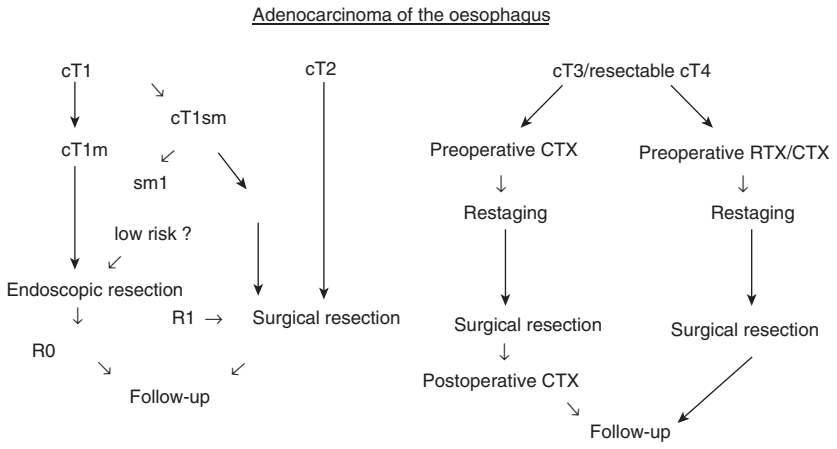

Figure 1: S3 guideline diagnostics and treatment of SCC and AC of the esophagus. Adapted from Porschen et al. [1].

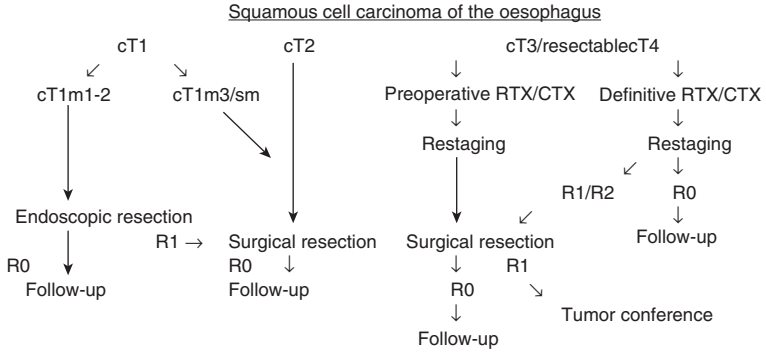

Figure 2: S3 guideline diagnostics and treatment of SCC and AC of the esophagus. Adapted from Hölscher [2].

longer (>2 cm) lesions or to achieve wider resection margins lead to a very high rate (50%) of stenosis with the necessity of multiple dilatations. Therefore, combined with doubts on radicality, this might be an approach into a dead-end street.

If an endoscopic resection was not successful, for example, because of microscopic residual tumor (R1) or deeper than mucosal infiltration with a risk of lymphatic metastasis or due to intractable stenosis, surgery is indicated. However, the operation should be done within due time. First data on time interval have shown prognostic disadvantages for patients with surgical resection after 6–12 months between endoscopic resection and definitive surgery [8].

cT2

In cT2NxM0 carcinomas, primary surgery is indicated. The guideline offers only the possibility of neoadjuvant therapy, especially in young patients with an individualized indication [9]. However, current studies show no prognostic benefit for neoadjuvant treatment in cT1 or cT2N0M0 esophageal cancer [10, 11]. The study of Markar et al. analyzed a database of 2944 consecutive patients for T2N0M0 and compared a group of 285 patients with primary surgery (S) to 70 with neoadjuvant treatment followed by surgery (NS). There was no significant difference in the 5-year survival between both groups (40% NS and 38% S). Further, 50% of the primary surgery group classified as cT2cN0 showed pN+ in the surgical specimen. From these, 20% were pN2 or pN3. This again underlines the unreliability of clinical N staging.

cT3/resectable cT4

In advanced esophageal cancer, either AC or SCC neoadjuvant therapy is strongly recommended in all international S3 guidelines [1, 2, 12] (Figures 1 and 2). For SCC

only, radiochemotherapy (RTX) is indicated, whereas in AC both chemotherapy (CTX) and RTX (RTX/CTX) are effective [13, 14]. The metaanalysis of Sjöquist or Ronellenfitsch and Burmeister and the Stahl trial on esophageal AC reported data on a slightly better survival after RTX/CTX versus CTX [15–18]. The prospective randomized Scandinavian trial on this matter, including SCC and AC and cT1 to cT3 carcinomas, showed that neoadjuvant RTX/CTX results in a higher histological complete response rate, a higher R0 resection rate, and a lower frequency of lymph node metastases compared to CTX. However, there was no significantly improved 3-year survival, which was in the intention-to-treat analysis 49% in the CTX arm and 47% in the RTX/CTX arm [19].

Individualization of treatment based on response

New approaches in neoadjuvant treatment are individualization based on response.

Via pretherapeutic endoscopic biopsies from the primary tumor and determination of a combination of molecular markers, a prediction of nonresponse is possible with a positive predictive value of 89% for minor histopathological response of the tumor according to our prospective Cologne Esophageal Response Prediction (CERP) study [20]. Minor histopathological response means that less than 10% vital tumor cells are detected by the pathologist [13, 14]. This prediction should identify the nonresponders in whom primary surgery could be performed to avoid time delay and side effects of a noneffective induction therapy. This prediction is also possible from liquid biopsies, which mean molecular markers from blood samples [21–23].

Our concept in the prospective CERP study, however, was based on an older RTX protocol with 5-FU, cisplatin, and 40 Gy radiation. Therefore, this has to be repeated based on a modern protocol such as in the CROSS study with RTX/CTX or FLOT [24–26].

The other approach is not based on prediction but clinical detection of response by endoscopy with biopsies, CT scan, or positron emission tomography (PET)-CT. The aim is to omit surgery in clinical complete responders and add more RTX/CTX as a definite treatment. In cases of recurrence salvage, surgery should be performed. A trial with this new approach is already in preparation in The Netherlands. The problem of this strategy is that the clinical detection of "complete" response is very unsafe. The accuracy of relief of dysphagia as a sign of response is low [27]. The accuracy of endoscopy with biopsies is only about 50%, as residuals of the tumor are often in the esophageal wall and not only at the inner surface [27–31]. CT scan cannot exactly differentiate between scar and residual cancer. PET-CT is influenced by inflammation and scaring in the radiated area, and several trials have shown that the predictive value of PET-CT for response during neoadjuvant RTX/CTX is insufficient for routine clinical application [32–35].

In a French study of 222 patients who had complete clinical response after neoadjuvant treatment, 59 patients who refused surgery were compared to 118 patients who had complete clinical response and esophagectomy [36]. The latter group showed residual tumor in 35% and in a median follow-up of >3 years a significantly better outcome than the group without surgery (Table 1). Therefore, this new approach of avoiding surgery in so-called clinically complete responders after neoadjuvant therapy bears a significant risk of coming too late and should be applied with considerable caution.

Individualization of treatment of Barrett's esophagus

Novel genetic risk variants for the development of Barrett's esophagus and esophageal AC have been found by genomic analysis of more than 6000 patients with Barrett's esophagus and more than 4000 esophageal AC [37]. Eight new

Table 1: Esophagectomy in patients with clinical complete response after neoadjuvant therapy.

	RTX/CTX	RTX/CTX+OP	p-Value
Number of patients	59	118	
Median survival (months)	31	83	0.001
Recurrence rate	51%	33%	0.021
Time of recurrence after end of treatment (months)	7.8	19	0.002
Locoregional recurrence	47%	16%	0.008

Matched pairs according to age, gender, site of tumor, TNM stage, histology, nutritional status, and ASA score of 222 patients with clinical complete response after RTX/CTX [36].

risk loci were identified. By these genetic markers, the prediction of malignant degeneration of Barrett's esophagus seems possible and this can represent a tool for individualized surveillance with endoscopic biopsies.

Oligometastasis

The achievements of multimodal treatment have led to the question if patients with limited resectable distant metastases should be included in protocols with curative intent. This comes from the FLOT trial in gastric cancer, which showed that a group with neoadjuvant CTX and resection of the primary tumor as well as limited metastases had a significantly better outcome than those patients without surgery [25, 38]. Therefore, the new RENAISSANCE trial has been set up to analyze this question in a prospective randomized fashion including patients with AC of the esophagus and the esophagogastric junction (AIO-STO-0215).

Extent of resection

The S3 guideline favors definitely transthoracic en bloc esophagectomy for AC or SCC of the esophagus [2]. This is based on the trials of Omloo or Kutup, which show prognostic advantages of this radical extent compared to transhiatal esophagectomy [39, 40]. For types II and III AC of the esophagogastric junction, transhiatally extended total gastrectomy with distal esophageal resection is favored if R0 resection with a sufficient safety margin can be achieved [41]. This has been approved by the 10-year follow-up results of the randomized clinical trial comparing left thoracoabdominal and abdominal transhiatal approaches to total gastrectomy [42]. Only if the infiltration of the distal esophagus is too extended for complete resection by an abdominal transhiatal approach that transthoracic esophagectomy with resection of the upper stomach and pull-up of a narrow gastric conduit should be applied [2]. However, the question as to which is the best extent of resection for type II AC, transhiatal with extended gastrectomy and distal esophageal resection or transthoracic esophagectomy with upper pole gastric resection, and gastric pull-up is not solved yet, as no prospective randomized trial comparing both strategies has been conducted.

New approaches to reduce the luminal extent of resection or the extent of lymphadenectomy after clinical response to neoadjuvant treatment are under discussion. However, they have the same shortcomings and risks as mentioned above for trials to avoid surgery completely in case of "complete" clinical response after induction therapy.

Total MIO/hybrid/open

There are different new approaches in MIO for esophageal cancer concerning approach and anastomotic technique.
Total minimally invasive

- Laparoscopic gastrolysis, thoracoscopic esophagectomy, and gastric pull-up with high intrathoracic anastomosis. This can be performed in conventional MIO technique (five trocars) mostly with circular stapler anastomosis or side-to-side with linear stapler anastomosis or with robotic surgery mostly with hand-sewn esophagogastrostomy.

Hybrid

- Laparoscopic gastrolysis, thoracoscopic esophagectomy, and open left cervical esophagogastrostomy hand-sewn or by circular stapler or side-to-side by linear stapler
- Laparoscopic gastrolysis, open transthoracic esophagectomy, and high intrathoracic esophagogastrostomy usually by circular stapler anastomosis
- Laparoscopic gastrolysis, open transthoracic esophagectomy, and left cervical esophagogastrostomy hand-sewn or by stapler
- Laparoscopic gastrolysis and transhiatal esophagectomy with cervical esophagogastrostomy hand-sewn or by stapler
- Open transabdominal gastrolysis and thoracoscopic esophagectomy with intrathoracic esophagogastrostomy usually by stapler

This diversity of procedures and the type of anastomosis shows that the ideal technique has not been found yet according to the profound clinical data. One randomized multicenter study (TIME trial) with limited patient numbers on the comparison of open versus laparoscopic/thoracoscopic esophagectomy (MIO) has shortcomings of comparability as the MIO group had single lumen tracheal intubation, whereas the patients with open esophagectomy had a double tracheal intubation with right-sided lung block. However, this trial showed significant differences in favor of MIO concerning the following [43]:

- Less rate of pulmonary complications
- Shorter stay on ICU
- Shorter duration of hospitalization

This direction points also to the reports of MIO versus historic controls of open esophagectomy [44, 45]. There

were no differences in postoperative mortality and short-term prognosis. The long-term results cannot be evaluated yet. The MIRO trial up to date published only as an ASCO abstract with the comparison of open esophagectomy versus laparoscopic gastrolysis and esophagectomy via thoracotomy and intrathoracic anastomosis (hybrid procedure) resulted in significant differences in favor of the hybrid approach concerning the following [46, 47] (Table 2):

- less postoperative morbidity
- less postoperative pulmonary complications
- reduced rates of postoperative Clavien-Dindo scores II–IV

This is supported by the results of the FREGAT retrospective study on 3009 French patients between 2010 and 2012 and the comparison of the hybrid technique to open surgery [48] (Table 3).

In the multivariate analysis, age ≥ 60 years, malnutrition, and cardiovascular comorbidity were independently associated with higher postoperative mortality, whereas the hybrid technique was combined with a decrease in mortality (OR 0.6; $p = 0.041$).

The only comparison between this hybrid technique and total MIO has been reported by Bonavina et al. [49]. On a propensity score-matched basis using the covariates age, sex, body mass index, forced expiration volume at 1 s (FEV1), Charlson comorbidity index, American Society of Anesthesiologists (ASA) score, histological tumor type, tumor site, pTNM stage, and neoadjuvant therapy, all postoperative outcomes including morbidity, mortality, nodal harvest, R0 resection rate, and 1-year survival rate were similar. Only the duration of operation was significantly longer in total MIO patients (Table 4).

The results of this report are parallel to our own experiences with 20 versus 20 propensity score-matched similar patients, with also no difference between both procedures [50]. In a total of 1200 consecutive hybrid esophagectomies of our own patients, we observed a 30-day mortality rate of 1%, a 90-day mortality rate of 3%, an anastomotic leak rate of 6.3%, and a normal postoperative course with a ventilation of less than 24 h in 77% of the patients.

These data from France, Italy, and Germany show that the hybrid procedure with laparoscopic gastric mobilization, abdominal lymphadenectomy, transthoracic esophagectomy, mediastinal lymphadenectomy, and high intrathoracic stapler anastomosis currently is the most justified technique. The laparoscopic dissective part is good to teach and safe to perform after a certain training period of about 20 procedures. The extent of lymphadenectomy is the same as in the open technique. A special trick is to place the suture for the hiatoplasty untied into the lower mediastinum and tie it only after transthoracic gastric pull-up to adjust the narrowing of the hiatal crus to the gastric conduit without stenosing the stomach.

The right transthoracic en bloc esophagectomy is radical, safe, and very reproducible. Lung adhesions can easily be severed and the lung can be palpated for lesions. The dissection in the upper mediastinum along the posterior tracheobronchial tree can be performed safely, especially in esophageal tumors at the trachea or tracheal bifurcation. This can be very demanding by scarring especially after induction RTX/CTX. Particularly, the stapler esophagogastrostomy in the upper mediastinum and the tailoring of the gastric conduit can be performed very safely. This procedure is good to teach stepwise. Thoracic pain control can effectively be achieved by peridural catheter.

Table 2: MIRO trial comparing hybrid to open esophagectomy [46].

	Hybrid	Open	p-Value
n	103	104	
Postoperative morbidity	35.9%	64.4%	0.001
30-day mortality	4.9%	4.9%	NS
Severe pulmonary complications	17.7%	30.1%	0.001
Not resected	1	1	
AC	63%	66%	NS
Resected lymph nodes (median)	21	22	NS

Table 3: FREGAT retrospective study results comparing hybrid to open esophagectomy [48].

	Hybrid	Open	p-Value
Patients total	663	2346	
30-day mortality	3.3%	5.7%	0.005
Hospital mortality	5.6%	8.1%	0.028
90-day mortality	6.9%	10.0%	0.016
Patients after propensity score matching	633	633	
30-day mortality	3.3%	5.9%	0.029

Table 4: Comparison of hybrid Ivor Lewis (laparoscopic/thoracotomy) to total MIO in prone position [49].

	Hybrid	Total MIO	p-Value
Total number of patients	197	93	
Patients after propensity scoring	80	80	
Hospital mortality	2.5%	3.7%	NS
Anastomotic leakage	12.5%	13.7%	NS
Duration of surgery (min)	300	330	0.01
1-year survival	92.3%	93.5%	NS

In contrast, thoracoscopic esophagectomy has a long learning curve of at least 60 procedures, and lung adhesions and the dissection of the tumor at the trachea or main bronchi can be very demanding. The anastomotic technique with the stapler is much more difficult than the open technique and affords at least a minithoracotomy for the insertion of a circular stapler and the removal of the specimen. If the anastomosis is placed in the neck (sort of hybrid) to avoid the mentioned problems of manufacturing the intrathoracic anastomosis by MIO, one encounters other difficulties, especially the definitely higher rate of anastomotic leakage. This was, for example, 22% or 30% in the CROSS trial in the two arms [24].

The operation time of total MIO and the one lung ventilation time is usually longer than the open technique. Considering the favorable results of the hybrid technique, it would be very difficult to prove in a prospectively randomized trial the superiority of total MIO compared to hybrid [49]. The target criteria would be very difficult to define and could only be postoperative pain, pulmonary problems, and duration of ICU stay and this would probably afford about 500 patients in each study arm.

Intraoperative evaluation of vascularization of gastric conduit

The most important factors for anastomotic healing of the esophagogastrostomy are no tension and good vascularization of the conduit. A new achievement is the visualization of vascularization by laser-assisted fluorescent dye angiography (LAA) with indigo cyanine green. In a study of 144 patients with esophagogastric anastomosis, the leakage rate was 16.7% [51]. A leak was significantly less likely when the anastomosis was placed in an area of good perfusion compared to when the anastomosis was placed in an area of less robust perfusion by LAA (2% vs. 45%; $p < 0.0001$). This technique may contribute to reduced morbidity due to anastomotic insufficiency but has to be approved in further trials.

Management of postoperative complications

The two main complications after esophagectomy are still pneumonia and anastomotic leakage. A new study has shown that preoperative airway colonization before transthoracic esophagectomy predicts postoperative pulmonary complications [52]. In 20% of 64 study patients, the pathological colonization of the bronchial airways could be proven before operation. The modern postoperative management includes all measures to avoid pulmonary infections by preoperative lung training, MIO, effective pain control by peridural catheter for good breathing and coughing, early mobilization, and, maybe in selected patients, preoperative antibiotic therapy.

The management of anastomotic leaks is based on rapid diagnostics with endoscopy and spiral CT scan. Except for very early noncontained insufficiencies or conduit necrosis, which need reoperation, the treatment of choice today is endoscopic sealing of the leak by stent or the endovacuum swamp (VAC) [53, 54]. Most leaks can successfully be controlled by these means.

Standardized documentation of complications after esophagectomy

A really new and important achievement is the International Consensus on Standardization of Data Collection for Complications Associated with Esophagectomy. Representatives of the leading centers for esophageal surgery from different countries [Esophagectomy Complications Consensus Group (ECCG)] under the direction of Don Low from Seattle have developed this basis for documentation. The reason is that in the literature the definitions for complications of esophagectomy are lacking or varied enormously. Consequently, a meaningful comparison of postoperative results from different countries is not possible. In the ECCG, the definitions have been discussed in detail and consented and published in 2015 [55]. The start of data collection in 2016 has shown that the database is appropriate and easy to handle. Up to September 21, 2016, 2087 patients with esophagectomy were included under the prerequisite that each esophagectomy of the participating centers is continuously documented to avoid selection bias [56]. The analysis of these reliable data will result in further important publications on this topic.

Enhanced recovery after esophagectomy

The concept of ERAS has been established in colorectal surgery and also applied for esophageal resection [57, 58]. This program includes especially detailed preoperative

information and preparation of the patient, minimally invasive surgery, intraoperative heart time volume orientated fluid management, consequent intraoperative and postoperative pain control via peridural catheter, extubation in the operating theater, no gastric tube, early oral feeding, intensive mobilization of the patient by physiotherapists starting on the day of operation, no abdominal drains, and early removal of thoracic drainages.

This program is possible but affords investments in manpower and convinced acceptance of all specialties that treat the patient in the perioperative period. The early discharge of the patient also implies the necessity of ambulant observation and continuous contact to avoid overlooking late complications and the necessity of rehospitalization. Therefore, these concepts still have to prove their significance in clinical routine for being equal or better compared to conventional postoperative treatments.

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Author Contributions

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Supplemental Material: The article (DOI: 10.1515/iss-2016-0020) offers reviewer assessments as supplementary material.

Reviewer Assessment **Open Access**

Arnulf H. Hölscher* and Benjamin Babic

New approaches in esophageal carcinomas

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Reviewers' Comments to Original Submission

Reviewer 1: Hans-Joachim Meyer

Sep 12, 2016

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	N/A

Custom Review Question(s)	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	5 - High/Yes
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:

- Please find out one way of orthography for esophageal vs. oesophageal (page 1 and 9, table 1)
- Check page 9: ..in listing operative procedures with (instead of sith)
- Are less than <10% vital tumor cells really minor hostpathological response (according to Keller it is score 1B)?
- Review the comment of table 1 (page 7): Do you mean really instead or in case of ?
- Table 2 (page 10): The prognosis is not stated

Reviewer 2: anonymous

Sep 21, 2016

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	80

Custom Review Question(s)	Response
Is the subject area appropriate for you?	3
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	4
Are units and terminology used correctly?	3
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:

This paper is a very fine review about the current multimodality therapy of esophageal cancer, entitled „New Approaches in Esophageal Carcinomas". Therefore, I have no major points of criticism.
However, the authors discussed the paper of Biere et al. published in 2012 and highlighted the findings about the lower rate of pulmonary complications, shorter stay on ICU and duration of hospitalization in esophageal cancer patients undergoing minimally invasive compared with open esophagectomy. Nevertheless, it is important to mention that in this trial, patients of the minimally invasive esophagectomy group received a single-lumen tracheal intubation whereas patients in the open esophagectomy group had a double tracheal intubation with right-sided lung block. Therefore, these two groups can hardly be compared regarding pulmonary complications and the authors should add this information to the manuscript.

Authors' Response to Reviewer Comments

Oct 11, 2016

Dear Prof. Jaehne,

all required corrections and additions to reviewers have been fulfilled.

Thank you for the good critique.

Reviewers' Comments to Revision

Reviewer 1: Hans-Joachim Meyer

Oct 18, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	N/A

Custom Review Question(s)	Response
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	5 - High/Yes
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	5 - High/Yes
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	5 - High/Yes
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	5 - High/Yes
Please rate the appropriateness of the figures and tables.	4
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:
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Reviewer 2: anonymous

Oct 11, 2016

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	75

Custom Review Question(s)	Response
Is the subject area appropriate for you?	4
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	3
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	3
Are units and terminology used correctly?	4
Is the number of cases adequate?	N/A
Are the experimental methods/clinical studies adequate?	N/A
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	3
Please rate the practical significance.	3
Please rate the accuracy of methods.	N/A
Please rate the statistical evaluation and quality control.	N/A
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	3
Please judge the overall scientific quality of the manuscript.	4
Are you willing to review the revision of this manuscript?	Yes

Comments to Author:
Accept the paper in the current form.