Endoscopic full-thickness resection and its treatment alternatives in difficult-to-treat lesions of the lower gastrointestinal tract: a cost-effectiveness analysis

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ABSTRACT
Objective Endoscopic full-thickness resection (EFTR) has shown efficacy and safety in the colorectum. The aim of this analysis was to investigate whether EFTR is cost-effective in comparison with surgical and endoscopic treatment alternatives.

Design Real data from the study cohort of the prospective, single-arm WALL RESECT study were used. A simulated comparison arm was created based on a survey that included suggested treatment alternatives to EFTR of the respective lesions. Treatment costs and reimbursement were calculated in euro according to the coding rules of 2017 and 2019 (EFTR). R0 resection rate was used as a measure of effectiveness. To assess cost-effectiveness, the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER) were determined. Calculations were made both from the perspective of the care provider as well as of the payer.

Results The cost per case was €2852.20 for the EFTR group, €3708.98 for EFTR, €1712 for the standard endoscopic resection (SER) group, and €5828 for the pooled alternative treatment to EFTR. From the perspective of the care provider, the ACER (mean cost per R0 resection) was €3708.98 for EFTR, €1712 for SER, €3115.10 for surgical treatment and €1712 for the standard endoscopic resection (SER) devices but lower than surgical devices.

Conclusion EFTR is cost-effective in comparison with surgical and endoscopic treatment alternatives in the colorectum.

INTRODUCTION
Colorectal cancer is the third most common type of cancer and the second most common cause of cancer-related deaths worldwide. Screening programmes for early detection of premalignant and malignant lesions led to a significant reduction in cancer-related mortality. With more intense screening more lesions are detected, which automatically creates the need for removal. Standard endoscopic resections (SER) such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are well established and sufficient for the vast majority of lesions. However, SER of non-lifting lesions and lesions located at difficult anatomical locations was shown to have a significantly higher failure rate.

What is already known about this subject?
• Endoscopic full-thickness resection (EFTR) has shown clinical efficacy and safety in difficult-to-treat lesions in the colorectum.
• The cost of the full-thickness resection device is higher than the cost of standard endoscopic resection (SER) devices but lower than surgical devices.
• Cost-effectiveness analyses on treatment with EFTR compared with treatment alternatives do not exist.

What are the new findings?
• EFTR leads to an almost 60% reduction in cost per R0 resection (average cost-effectiveness ratio) compared with surgery.
• To achieve an additional R0 resection by surgical treatment compared with EFTR (incremental cost-effectiveness ratio), an additional cost of €27 000 is necessary.
• These findings are consistent both from the perspective of the care provider as well as the payer.

How might it impact on clinical practice in the foreseeable future?
• In terms of cost-effectiveness, EFTR should be considered first before patients with difficult-to-treat lesions in the colorectum are sent to surgical treatment.
locations (eg, appendiceal orifice) is associated with increased complication rates or incomplete resection. These types of lesions are therefore often referred to as a huge economic challenge.

The efficacy and safety of endoscopic full-thickness resection (EFTR) of non-lifting and other difficult-to-treat lesions have been demonstrated in multiple retrospective studies and in one prospective study. The cost of the device is markedly higher than SER devices, but lower than surgical treatment. The aim of the present analysis was to evaluate whether EFTR is cost-effective in comparison with SER as well as surgical treatment.

METHODS Study population
To calculate the cost of EFTR, we analysed the study cohort of the WALL RESECT trial (NCT02362126). In this single-arm, multicentre, prospective study, 181 patients with ‘difficult-to-treat’ adenomas (eg, non-lifting and/or challenging anatomical location), early adenocarcinomas and subepithelial tumours in the colorectum were treated with EFTR. The primary endpoints of the study, en bloc and R0 resection rate, were achieved in 89.5% and 76.9%, respectively. Written, informed consent was obtained from each patient included in the study.

Simulation second study arm based on a survey of endoscopists
With the WALL RESECT study being single-armed, a second study arm was created based on treatment simulation. In order to compare different treatment modalities, a case report form (CRF) was created and sent to each participating centre of the WALL RESECT trial. Endoscopists at the respective location reviewed the endoscopic images and their case-relevant data and decided which treatment modality they would have chosen if EFTR were not available. Treatment alternatives included SER, such as EMR, thermal methods and ESD, as well as surgical resection. The CRF was filled out in a pseudonymised fashion.

Informed consent had already been obtained within the WALL RESECT study.

Determination of case costs and reimbursement
A certified online IT tool (G-DRG-Report Browser) was used to determine the reimbursement rate for each patient (http://drg.uni-muenster.de/index.php). Therefore, the code of the International Classification of Diseases (ICD-10) and the specific code for the procedure performed (Operationen- und Prozeduren schlüssel (OPS) code) in each patient in both groups were put into the Web Grouper. Together with the predefined mean length of hospital stay (‘mittlere Grenzverweildauer’) the DRG, which accounts for reimbursement, was calculated.

In the comparison arm, the DRG codes of 2017 were used because this was the year the WALL RESECT study was performed. For the EFTR arm, the DRG codes of 2019 were used, as reimbursement for EFTR was increased that year.

To calculate the cost per case, another certified online IT tool (G-DRG-Report Browser) was used (https://www.g-drg.de/G-DRG-System_2019/Absschlussbericht_zur_Weiterentwicklung_des_G-DRG-Systems_und_Report_Browser). This was done by filling in the respective DRG, ICD-10 and OPS code into the browser. The data of the G-DRG-Report Browser 2019 derive from the data that were sent in to InEK (authority managing the German DRG system) by certified hospitals (‘Kalkulationshäuser’) in 2017. Grouping was performed following the rules of G-DRG 2017/2019 version. The main and secondary diagnoses are shown according to ICD-10-german modification (GM) 2017 version and the procedures according to OPS 2017 version (‘G-DRG-Report Browser 2019, InEK GmbH’).

As reimbursement for the EFTR group was taken from 2019, the cost per patient case would ideally also have been calculated from 2019. Unfortunately, these data will be first published by InEK in 2021. To overcome this problem, costs for EFTR cases from the University of Freiburg between 2017 and 2019, which were reported to InEK, were used for the analysis.

With the cost of each patient case, the mean cost for each treatment modality (EMR, ESD, laparoscopic surgery, transanal endoscopic microsurgery (TEM), EFTR) could be calculated. In the next step, the mean cost for each treatment path (SER, surgical treatment and casemix alternative) was determined. This was done in the following fashion: for SER, the mean costs of EMR and ESD were used. For calculation of the surgical treatment, laparoscopic surgery and TEM were taken together. The mean costs of endoscopic and surgical treatments were subsumed as the casemix alternative.

Determination of effectiveness
The R0 resection rate was defined as the efficacy parameter to determine cost-effectiveness. The R0 rate of EFTR in the WALL RESECT trial was 76.9% (0.769). To determine the efficacy of the therapeutic alternatives to EFTR, a selective literature review was performed in PubMed and Cochrane databases identifying the largest studies comparing resection techniques and R0 rates. The respective rates regarding SER found in the literature were 42.3% (0.423) for EMR and 74.6% (0.746) for ESD. For the TEM, a rate of 88.5% (0.885) had been reported. In order to compare all SER methods (EMR+ESD), all surgical resection methods (laparoscopic surgery+TEM) and all alternative methods (endoscopic and surgical;
ICER expresses the additional costs of a treatment alternative for improvement in the investigated outcome. In our study, these are the incremental costs for the alternative treatment to EFTR required to achieve an R0 resection.

ICER is calculated with the following computational formula:

\[
\text{ICER} = \frac{\text{mean costs intervention} - \text{mean costs control}}{\text{effect intervention} - \text{effect control}}
\]

The mean costs were the total costs of the respective treatment modality divided by the number of patients in each group. For the calculation of cost-effectiveness, the SER methods (EMR and ESD) as well as the surgical resection methods (laparoscopic resection and TEM) were taken together. Furthermore, cost-effectiveness was calculated for the casemix alternative to compare EFTR with all alternatives.

### RESULTS

#### Comparative study arm/endoscopist survey

From 181 patients of the study cohort, 180 responses were included for further analysis. In one patient, the investigator recommended solely ‘thermal ablation’ as alternative treatment of choice; thus, the primary endpoint R0 resection could not be evaluated. From the remaining 180 patients, the endoscopists recommended surgical treatment in 59% (106 of 180) of cases. Thereof, 97% (103 of 106) were laparoscopic resections and 3% (3 of 106) TEM. In 41% (74 of 180) of cases, an endoscopic resection was proposed. Thereof, 61% (45 of 74) were EMR and 39% (29 of 74) were ESD.

#### Costs from the perspective of the care provider

Costs per case were derived from the DRG-Report Browser 2019 which represent costs of the respective treatment alternative for the year 2017. The costs for the EFTR treatment were derived from University Hospital Freiburg and represent the mean costs from years 2017 to mid-2019. The mean cost for EFTR was €2852.20. The cost per surgical treatment (laparoscopic surgery and TEM) was €8895 and for SER €1712. All alternative treatment strategies ‘casemix alternative’ (OP laparoscopic surgery, TEM, ESD, and EMR) were calculated as €5828 per case. The results are shown in figure 1.

#### Costs from the perspective of the third-party

According to the German DRG System, reimbursement for EFTR is €3069. For surgical treatment €9619 was calculated. The cost per case for SER is €1646. The cost for the casemix alternative is €8437. The results are shown in figure 1.

#### Cost-effectiveness analysis: care provider viewpoint

**Average cost-effectiveness ratio**

The mean cost per R0 resection is €3708.98 in the EFTR group and €3069 in the surgical group. In the SER group, the cost per R0 resection is €3115.10. In the casemix alternative group, including all treatment modalities (laparoscopic and TEM) was €1038.92. All alternative treatment strategies ‘casemix alternative’ (OP laparoscopic surgery, TEM, ESD, and EMR) were calculated as €5828 per case. The results are shown in figure 1.

### Calculation of cost-effectiveness

For assessment of cost-effectiveness, the average cost-effectiveness ratio (ACER) and the incremental cost-effectiveness ratio (ICER) were calculated. ACER expresses the mean costs for the investigated outcome. In our study, ACER describes the mean costs per successful R0 resection in the different treatment modalities.

ACER is calculated with the following computational formula:

\[
\text{ACER} = \frac{\text{mean costs intervention}}{\text{effect intervention}}
\]

| Treatment                             | n (N=180) | Efficacy (%) |
|---------------------------------------|-----------|--------------|
| Surgical oncological resection (laparoscopic) | 103       | 100 (assumed) |
| TEM                                   | 3         | 88.5 (Arezzo et al, 2014)¹⁰ |
| EMR                                   | 45        | 42.3 (Fuiya et al, 2015)⁹ |
| ESD                                   | 29        | 74.6 (Arezzo et al, 2014)¹⁰ |
| Surgical treatment (laparoscopic and TEM) | 106       | 99.7 (calculated) |
| SER (EMR+ESD)                         | 74        | 54.9 (calculated) |
| Casemix alternative                   | 180       | 81.2 (calculated) |

The combined effectiveness of surgical treatment, SER and casemix alternative was calculated by multiplication of the number of patients in each modality (eg, 45 EMR cases for SER) with the respective R0 resection rate (0.423) as the first step. In the second step, this result would be summed up to the result of the other modalities (eg, ESD+EMR result for the SER methods) and divided by the number of patients in this group of resection method (eg, 74 patients in the SER group). Overall efficacy of surgical treatment and casemix alternative was performed in the same manner.

EFTR, endoscopic full-thickness resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SER, standard endoscopic resection; TEM, transanal endoscopic microsurgery.
alternatives except EFTR, the mean cost per R0 resection is €7169.30. The results are shown in figure 2.

**Incremental cost-effectiveness ratio**

In comparison with EFTR, the incremental cost for an additional R0 resection is €5196.47, if SER is performed. The cost for the surgical approach is €26533.13 and for the casemix alternative €67768.62. The results are shown in figure 3.

**Cost-effectiveness analysis: health insurance reimbursement viewpoint**

**Average cost-effectiveness viewpoint**

From the perspective of the health insurance, the cost per R0 resection is €3990.90 in the EFTR group. In the SER group, the cost is €2995.01 and in the surgical treatment group €9650.41. In the casemix alternative, the cost per R0 resection is €10378.75. The results are shown in figure 2.

**Incremental cost-effectiveness ratio**

The ICER of SER in comparison with EFTR is €6485.31. The surgical approach costs an additional €28760.20. For the casemix alternative €122246.96 is necessary for an additional R0 resection. The results are shown in figure 3.

**DISCUSSION**

With technical endoscopic progress, patient care has constantly improved over the years; however, as with any technical innovation, this is associated with higher costs. Therefore, the efficacy of new methods and devices needs to be evaluated in relation to their costs. To our knowledge, this is the first cost-effectiveness analysis (CEA) for EFTR. Our results demonstrate that EFTR for difficult-to-treat lesions in the colorectum is cost-effective in comparison with SER as well as surgical therapy. Furthermore, the results are consistent when analysed from the perspective of the care provider as well as of the payer.
For our analysis, a simulated control arm was created. This was necessary as to date no randomised controlled trial (RCT) investigating EFTR versus alternative treatments has been published. In our survey, endoscopists proposed surgical treatment as the likely alternative to EFTR in the majority (59%) of cases as opposed to SER via EMR or ESD (41%). All lesions within the WALL RESECT trial were ‘difficult-to-resect’ lesions (eg, non-lifting adenomas) exhibiting a high risk of perforation or incomplete resection when treated with SER. Therefore, it may be surprising that SER was suggested in 41% of cases. However, the suggestions were made by expert endoscopists who might have decided towards an advanced endoscopic procedure more generously.

Regarding the costs for each treatment modality, it was not surprising that the cost of EFTR is 40% above SER (€2852 vs €1712). This is due to the cost of the device (in Germany €849 plus value-added tax). However, the cost of EFTR was roughly one-third of the cost of surgery (€2852 vs €8895). This reflects the minimally invasive nature of EFTR compared with laparoscopic or open surgical operations.

While costs for endoscopic resection and surgical therapy were taken from official and certified tools (Web Grouper and DRG-Report Browser), the factual costs of the EFTR procedure for the year 2019 that are determined in a representative cross-section of hospitals have not been published yet by InEK, the administrator of the DRG system. Reimbursement of the procedure changed in 2019; thus, these data should have been used for calculation. To overcome this problem, the mean case costs for EFTR per case in our home institution (University Hospital of Freiburg, Germany) in the time between 2017 and 2019 were used as a surrogate. In 2019, an economic analysis of the cost of EFTR in Germany (presented at the annual conference of the German Society for Digestive Diseases 2019) obtained from different endoscopic centres reported €3058 per case. As this is only 7% above our number and therefore in the same range, our calculated €2852 seems to be a realistic number.14

In our analysis, we chose the R0 rate as a means to determine effectiveness, as this is the most objective parameter to assess curative resection and treatment success. Furthermore, the R0 rate can be compared with the treatment alternatives of EFTR, as high-quality meta-analyses and therapeutic success rates exist for these procedures.10,15 The R0 rate for surgical colonic resection was assumed to be 100%. However, the patient cohorts of these studies are not equal: the WALL RESECT study included only ‘difficult-to-resect’ lesions (mainly non-lifting), while the studies mentioned above included primarily treatment-naïve lesions. Larger studies on SER on non-lifting lesions do not exist. Hence, it is reasonable to assume that in these indications real R0 rates of SER would be lower and therefore cost-effectiveness would be even worse.

For measuring cost-effectiveness, ACER and ICER were determined. The analysis was performed both from the perspective of the care provider (hospital) as well as the reimbursement authority (health insurance). ACER expresses the mean cost per R0 resection. For both investigated perspectives, our results reveal that costs are much lower for EFTR compared with the surgical alternative. Although the effectiveness of the surgical approach in terms of radicality can be considered to be higher, EFTR is cost-effective. An R0 resection by EFTR leads to nearly 60% reduction in costs for the care provider (€3708.98/€8924.05=0.42) and for the health insurance (€3990.90/€9650.41=0.41). Compared with SER, EFTR leads to marginally higher costs per R0 resection. As explained above, comparing EFTR with SER has limitations as the investigated ‘difficult’ lesions in the WALL RESECT study are not well studied for EMR and ESD. However, in comparison with all treatment alternatives (‘casemix alternative’), we calculated 49% and 64% reduction in costs (similar to the surgical alternatives) (figure 2).

ICER expresses the additional costs for an additional increase in the designated outcome. In our analysis, it expresses the additional costs that are necessary for an additional R0 resection. As shown in figure 3, all alternatives to EFTR result in additional costs. While SER results in a modest increase (€5196.47 and €6485.31), additional €26533.13 and €28760.20 per R0 resection are required in the surgical group. In the ‘casemix alternative’ group, additional costs were €67768.62 and €122 246.96, respectively.

An absolute threshold at which an ICER is thought to be cost-effective does not exist.16 In the literature the willingness-to-pay threshold ranges from 0 to $50000–$100000 and is highly subjective to the investigated outcome and the healthcare system for which the CEA is made.17–21 For our analysis, we assume that a more invasive treatment that produces at least €25000 more costs for an additional R0 resection cannot be regarded as being cost-effective.

For our analysis, we did not include costs of follow-up endoscopies or further treatment arising from recurrence or from adverse events. This was done due to the following reasons: first, reliable recurrence rates and long-term follow-up after EFTR do not exist. Follow-up in the WALL RESECT trial was only 12 weeks. Second, the lesions of our patient cohort were heterogeneous, including adenomas, carcinomas and neuroendocrine tumours, with different biological features and recurrent rates. Third, treatment of recurrent lesions is not standardised and ranges from re-EFTR to snare polypectomy, to removal with a biopsy forceps, leading to highly variable costs. Fourth, management of severe complications and consecutive morbidity differs in every patient and depends on severity of complication, patients’ comorbidities and local expertise. We do not have reliable data on costs for such treatment and a hypothetical model would have been highly speculative. Moreover, in the WALL RESECT trial, 2.2% of patients required consecutive surgery due to complications. This rate is slightly
higher but still grossly comparable with the complication rates of EMR and ESD. On the other hand, complications after surgical resection (e.g., anastomotic leakage) are much more frequent (up to 15%–30%) and usually lead to higher morbidity. Hence, even if costs related to complications were added, ICER is still likely to favour EFTR compared with the group of treatment alternatives.

It is difficult to compare our results with other CEAs as this is the first one for this indication. The only previous CEA on SER compared EMR and ESD in laterally spreading lesions irrespective of location or lifting sign. In most analyses, as in the study by Bahin and colleagues, a decision tree model was created to compare different outcome scenarios. After each treatment path was filled with probabilities of occurrence, costs per predefined outcome were calculated. A potential bias of this approach is that the data for the probabilities of occurrence, which influence the costs most, are taken totally or at least in part from different studies. This harbours the risk of resulting in a very heterogeneous study population with uncontrolled confounders. This risk can be minimised by deriving data from RCTs with well-balanced patient cohorts as recently published.

For our analysis, we used a different approach than a decision tree: factual variables and outcome data derived from the only prospective study on EFTR treatment, and not from assumptions. The simulation of the control arm had to be performed due to the lack of RCTs in this setting. The strength of our study is that the very same clinician who actually performed the respective EFTR could review the different lesions and decide on a solid basis which treatment alternative he or she would have used instead of EFTR. In our view this approach reflects the clinical situation more precisely than a decision tree model.

In most CEAs, the costs per quality-adjusted life years are calculated and taken for healthcare decisions. Neither survival nor quality of life measurements were part of the WALL RESECT trial. In line with most of the recently published CEA, we calculated costs per defined outcome as the primary endpoint.

Our study has several limitations. First, the comparison arm of the study is based on simulation, so there is always a risk of a bias. Second, our analysis is specific to the German healthcare system and may therefore not be fully comparable with different healthcare systems in the world. Third, the estimated R0 rate for the SER methods is very low and likely due to the piecemeal resection in the respective study. If efficacy would have been measured as ‘freedom of recurrence’, efficacy would be higher (as proven in the Australian Colonic Endoscopic study). Nonetheless, we used the published R0 rate because of the possibility to match this with the endpoint of the WALL RESECT study. Furthermore, as described above, an endpoint such as freedom of recurrence cannot be determined reliably as such data do not exist for EFTR. Fourth, costs of complications and follow-up were not included. This is mainly due to lack of an RCT and the short follow-up period. In an ideal CEA, all treatment-related and hospital stay-related costs would have been calculated.

In conclusion, our data indicate that EFTR for difficult-to-treat lesions of the colorectum is cost-effective compared with surgical and endoscopic treatment alternatives. The results are consistent both from a care provider as well as from a third-party payer perspective. RCTs and long-term follow-up are needed to further assess the cost-effectiveness of EFTR.
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