BJS Open, 2025, zraf061
https://doi.org/10.1093/bjsopen/zraf061
Original Article

Intrathoracic *versus* cervical anastomosis after totally or hybrid minimally invasive transthoracic oesophagectomy for oesophageal cancer: cost-effectiveness analysis alongside the randomized ICAN trial

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Abstract

Background: There is a worldwide trend towards minimally invasive oesophagectomy with intrathoracic anastomosis in oesophageal cancer surgery. Minimally invasive oesophagectomy with intrathoracic anastomosis has been shown to result in fewer anastomotic leaks, but cost-effectiveness is yet to be established. The aim of this study was to determine the cost-effectiveness of transthoracic minimally invasive oesophagectomy with intrathoracic anastomosis compared with cervical anastomosis.

Methods: A prospective economic evaluation was performed alongside the ICAN trial, a randomized clinical superiority trial. Patients with mid/distal oesophageal or gastro-oesophageal junction cancer were randomly assigned to transthoracic minimally invasive oesophagectomy with either intrathoracic or cervical anastomosis. Quality-adjusted life-years, mean healthcare, and societal costs were assessed for both groups at 9 and 21 months after surgery.

Results: A total of 245 patients randomized for transthoracic minimally invasive oesophagectomy with either intrathoracic (122) or cervical (123) anastomosis were included in the cost-effectiveness analysis. After 9 months, the intrathoracic group yielded 0.58 (95% confidence interval (c.i.) 0.55 to 0.61) quality-adjusted life-years per patient, compared with 0.56 (0.52 to 0.58) quality-adjusted life-years for the cervical group. After 9 months, both mean healthcare costs (20 573 (95% c.i. 17 623 to 24 177) *versus* 28 039 (23 574 to 33 116) euros), and societal costs (24 590 (21 237 to 29 074) *versus* 33 383 (27 885 to 38 805) euros), per patient were lower in the intrathoracic anastomosis group. Similarly, at 21 months no statistically significant difference was found (mean difference 0.08 (−0.05 to 0.2) quality-adjusted life-years), whereas minimally invasive oesophagectomy with intrathoracic anastomosis was less costly than that with cervical anastomosis (mean difference −9930 (−16 301 to −2521) euros). The higher costs in the cervical anastomosis group were mainly due to longer lengths of stay owing to complications.

Conclusion: Transthoracic minimally invasive oesophagectomy with intrathoracic anastomosis was found to be cost-effective compared with transthoracic minimally invasive oesophagectomy with cervical anastomosis.

Introduction

Oesophageal cancer ranks seventh in the top ten most common cancers worldwide and is the sixth most common cause of cancer-associated death[1]. The incidence of oesophageal adenocarcinoma is expected to rise in the coming years, especially in high-income countries[2]. Currently, transthoracic oesophagectomy with intrathoracic or cervical anastomosis has become the standard technique in patients with oesophageal cancer. There is a worldwide trend towards more minimally invasive surgery and intrathoracic anastomosis in oesophageal cancer surgery[3–5]. In the Netherlands, transthoracic minimally invasive oesophagectomy (MIE) with intrathoracic anastomosis is the most frequently used technique to perform an oesophagectomy for oesophageal cancer[6]. However, insight into the cost-effectiveness of this technique compared with cervical anastomosis is lacking.

It is often claimed that cervical anastomotic leaks are more common but less severe compared with intrathoracic anastomotic leaks. Multiple non-randomized studies and systematic reviews

Received: October 19, 2024. **Revised:** February 27, 2025. **Accepted:** April 11, 2025

have compared clinical outcomes of MIE with cervical anastomosis to MIE with intrathoracic anastomosis in an attempt to support this hypothesis. Some studies have shown a higher rate of anastomotic leak after cervical anastomosis, but other studies have failed to show a significant difference[7–11]. Studies[12–15] addressing leak severity have also shown contradictory results. Due to a lack of high-quality evidence, strong recommendations regarding the preferred anastomotic location could not be made previously. The intrathoracic *versus* cervical anastomosis (ICAN) trial, a multicentre randomized clinical superiority trial, recently reported significant reductions in anastomotic leak rates and severe complications for transthoracic MIE with intrathoracic anastomosis compared with MIE with cervical anastomosis. The ICAN trial[16] also showed a lower incidence of laryngeal nerve palsy and a slightly better short-term quality of life in three subdomains for MIE with intrathoracic anastomosis. Due to these lower incidences of anastomotic leak and severe complications, it is expected that the trend towards MIE with intrathoracic anastomosis will further increase in the coming years. However, in the current times with rising concerns about the affordability of healthcare, the cost and resource use of MIE with intrathoracic anastomosis should be assessed to justify this shift.

The aim of this study was to determine the cost-effectiveness of transthoracic MIE with intrathoracic anastomosis compared with transthoracic MIE with cervical anastomosis, thereby contributing to evidence-based decision-making for the treatment of patients with curable oesophageal or gastro-oesophageal junction cancer.

Methods

Design

As stated in the ICAN study protocol, an economic evaluation was performed alongside the ICAN trial, a multicentre randomized clinical superiority trial performed in nine high-volume hospitals in the Netherlands, including five university medical centres and four non-academic teaching hospitals. Patients were assigned randomly (1 : 1) to transthoracic MIE with intrathoracic or cervical anastomosis. The ICAN study protocol[17] was published previously and was approved by the institutional review board of the Radboud University Medical Centre and all participating centres. All patients provided written informed consent. The ICAN trial is registered in the Dutch trial register (NL4183; NTR4333).

This economic evaluation is reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards guideline[18].

For further information about the trial design, sample size, randomization, data storage, and validation, see the ICAN main article[16] or study protocol[17].

Participants

Adult patients with histologically proven primary oesophageal adenocarcinoma or squamous cell carcinoma were screened for eligibility. Patients were eligible for participation in the study if the tumour was resectable (cT1b–4a N0–3 M0) and located in the mid-oesophagus (from the level of the carina to the distal oesophagus), distal oesophagus, or at the level of the gastro-oesophageal junction (Siewert levels I to II). According to national guidelines[17], patients received neoadjuvant chemoradiotherapy or perioperative chemotherapy.

Interventions

All patients underwent transthoracic MIE with either intrathoracic anastomosis or cervical anastomosis, by either a hybrid minimally invasive approach (laparoscopy and thoracotomy) or a totally minimally invasive approach (laparoscopy and thoracoscopy). A two-field lymph node dissection was performed in all patients. Anastomotic techniques and configuration (handsewn or stapled/end to end, end to side, side to side) could be chosen according to the surgeon's preference[16].

Measures of effectiveness

Quality-adjusted life-years (QALYs) were used to measure effectiveness. To determine QALYs, health-related quality of life (HRQoL) was measured using the EuroQol five-domain five-level questionnaire (EQ-5D-5L™; EuroQoL Group, Rotterdam, the Netherlands)[19]. Initially, it was planned to measure HRQoL at 3, 6, 12, and 24 months after surgery[17]. However, all patients had already completed the questionnaires at 3, 6, 9, and 21 months after surgery, as part of an ongoing registry, the Dutch Prospective Observational Cohort Study of Oesophageal-gastric cancer Patients (POCOP)[20]. To reduce patient burden, it was decided to use these measurements for the present study. Utility scores were calculated using the Dutch tariff for the five-level version of EQ-5D™[21]. Total utility scores over the 9- and 21-month periods were calculated by the area under the curve method[22]. After the first year of follow-up, QALYs were discounted at a rate of 1.5%[23].

Costs

The economic evaluation was conducted from both healthcare and societal perspectives. The healthcare perspective comprised the costs for the primary operation, (re)admission, (re)interventions, and imaging costs for 2 years after surgery. However, the costs for preoperative treatment, such as neoadjuvant therapy and preoperative imaging, and costs for disease recurrence and palliative care were not included as these were no different between the treatment arms.

The societal perspective, in addition to the healthcare costs, included travel costs, costs for home care, nursing home care/rehabilitation care, and paramedical care.

Costs due to productivity loss were not included in the societal perspective (*supplementary results*).

Resource use data were collected prospectively from clinician-registered case record forms (CRFs) and patient questionnaires. The CRFs covered the resources related to the operation (for example operating time, anastomotic configuration, stapler use, number of blood transfusions), hospital stay (for example duration of intensive care unit (ICU) (re)admission and surgical ward admission), complications (for example reinterventions, in case of anastomotic leakage additional imaging), and mortality.

The Institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire[24] and the iMTA Productivity Cost Questionnaire[25] were used. These questionnaires covered the productivity loss and the resource use related to travel and parking expenses, paramedical use (for example number of appointments with physical therapist/psychologist), home care (hours of home care), and admittance to a nursing home or rehabilitation centre. Both questionnaires were gathered from the POCOP registry and thus administered at 3, 6, 9, and 21 months. Data from both questionnaires were extrapolated to match the period between questionnaires.

Because it was assumed that most resources were to be used within 9 to 21 months, the data from the 12- and 24-month CRFs, respectively, were used as proxy for the 9- and 21-month resource use, to match the follow-up of the patient questionnaires.

Total costs were calculated by multiplying the resources used by the corresponding unit cost. Reference costs for hospital stay, (para)medical contacts, hours of home care, travel, and parking costs were based on the Dutch guideline for economic evaluation[23]. Stapler costs were based on the list price (for example Endo GIA™ ultra-universal stapler; Medtronic, Minneapolis, MN, USA). Complication and imaging costs were based on the Dutch Healthcare Authority and internal cost calculations of the Radboud University Medical Centre. (*Table S1*) Productivity costs were measured using the friction cost method, assuming a friction period of 85 days[23]. Costs occurring after the first year of follow-up were discounted at a rate of 4%[23].

Statistical analysis

Mean differences in costs and QALYs between transthoracic MIE with intrathoracic anastomosis and cervical anastomosis were calculated at 9 and 21 months. In accordance with the Professional Society for Health Economics and Outcomes Research guidelines[26], mean cost values were reported. Whether MIE with intrathoracic anastomosis was found to be more costly and more effective, or less costly and less effective, than cervical anastomosis, an incremental cost-effectiveness ratio was calculated to represent the additional costs per QALY gained, or the costs saved per QALY lost. Following the Dutch guideline for economic evaluation[23], a cost-effectiveness threshold of 80 000 euros (€) per QALY was used.

Missing data were addressed using single imputation nested in the bootstrap percentile method[27]. First, bootstrapping was used to generate 5000 incomplete data sets, and then a single completed data set was generated for every incomplete data set and analysed. A detailed description of the analyses is presented in the *supplementary methods*. Using the bootstrapping results, 95% confidence intervals (using the percentile method), cost-effectiveness planes, and acceptability curves were created, illustrating the probability of cost-effectiveness against different cost-effectiveness thresholds (range €0–120 000).

Statistical analyses were performed using R software version 4.3.2 (R Project for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 245 patients randomized for transthoracic MIE with either intrathoracic (122) or cervical (123) anastomosis were included in the cost-effectiveness analysis (*Fig. S1*). Baseline characteristics of the participants are presented in *Table S2*.

Effectiveness

On average, patients who underwent MIE with intrathoracic anastomosis gained 0.58 (95% confidence interval (c.i.) 0.55 to 0.61) QALYs compared with 0.56 (0.52 to 0.58) QALYs in the MIE with cervical anastomosis group in the first 9 months after surgery. The mean difference was 0.02 (−0.02 to 0.06) QALYs in favour of the MIE with intrathoracic anastomosis group.

After 21 months, the MIE with intrathoracic anastomosis group gained a mean of 1.19 (1.09 to 1.26) QALYs compared with 1.11 (1.00 to 1.19) QALYs in the MIE with cervical anastomosis group. The mean difference at 21 months was 0.08 (−0.05 to 0.2) QALYs in favour of the MIE with intrathoracic anastomosis group. Survival data and data regarding missing EQ-5D™ questionnaires are available in *supplementary results*.

Costs

The mean costs per patient from both healthcare and societal perspectives at 9 months are presented in *Table S3*. From a healthcare perspective, the mean costs per patient were €20 573 (95% c.i. 17 623 to 24 178) for MIE with intrathoracic anastomosis and €28 039 (23 574 to 33 116) for MIE with cervical anastomosis at 9 months, and this resulted in a cost difference of €−7466 (−13 400 to −1713) in favour of MIE with intrathoracic anastomosis. The biggest difference was noted in the cost of primary admission after surgery, a cost difference of €4497 in favour of the intrathoracic anastomosis group. This difference was explained by a longer length of stay in the cervical anastomosis group caused by prolonged hospital admission due to complications.

During the first year after oesophagectomy 59 patients were readmitted to hospital for a total of 69 times, with a mean length of stay of 16 days in the cervical anastomosis group. In the intrathoracic group, 35 patients were readmitted a total of 41 times, with a mean length of stay of 12 days. Readmission was related to primary surgery in 66 patients in the cervical anastomosis group *versus* 38 in the intrathoracic anastomosis group

From a societal perspective, the mean costs per patient were €24 590 (21 237 to 29 074) for MIE with intrathoracic anastomosis and €33 383 (27 885 to 38 805) for MIE with cervical anastomosis. This resulted in a cost difference of €−8793 (−15 081 to −1816) in favour of MIE with intrathoracic anastomosis at 9 months.

The mean costs per patient from both healthcare and societal perspectives at 21 months are shown in *Table S3*. From a healthcare perspective, the mean costs per patient at 21 months were €20 936 (17 961 to 24 581) for MIE with intrathoracic anastomosis and €28 989 (24 458 to 34 132) for MIE with cervical anastomosis. This resulted in a cost difference of €−8053 (−14 028 to −2308) in favour of MIE with intrathoracic anastomosis. Costs related to readmission in year 2 were the main reason for this small increase in difference. A total of 27 patients were readmitted: 13 patients in the cervical anastomosis group *versus* 14 in the intrathoracic anastomosis group. For 11 of these patients from both groups, the reason for readmission was related to primary treatment. Hospital readmission (non-ICU) was 117 days in total in the cervical anastomosis group *versus* 72 days in the intrathoracic group. In the cervical group, two patients were readmitted to the ICU (pneumonia and oesophageal discontinuity reversal; in total 20 days in ICU), whereas in the intrathoracic anastomosis group no patients were readmitted to the ICU. From a societal perspective, the mean costs per patient at 21 months were €25 661 (22 101 to 30 239) for MIE with intrathoracic anastomosis and €35 591 (29 686 to 40 987) for MIE with cervical anastomosis. This resulted in a cost difference of €−9931 (−16 301 to −2521) in favour of MIE with intrathoracic anastomosis.

Cost-effectiveness

After both 9 and 21 months of follow-up, MIE with intrathoracic anastomosis was found to be less costly than MIE with cervical anastomosis, and there was no statistically significant difference in QALYs. Hence, MIE with intrathoracic anastomosis was found to surpass MIE with cervical anastomosis (*Fig. 1*). From a societal perspective, MIE with intrathoracic anastomosis was cost-effective in at least 98% of the replications at any cost-effectiveness threshold between €0 and €120 000 per QALY (*Fig. 2*).

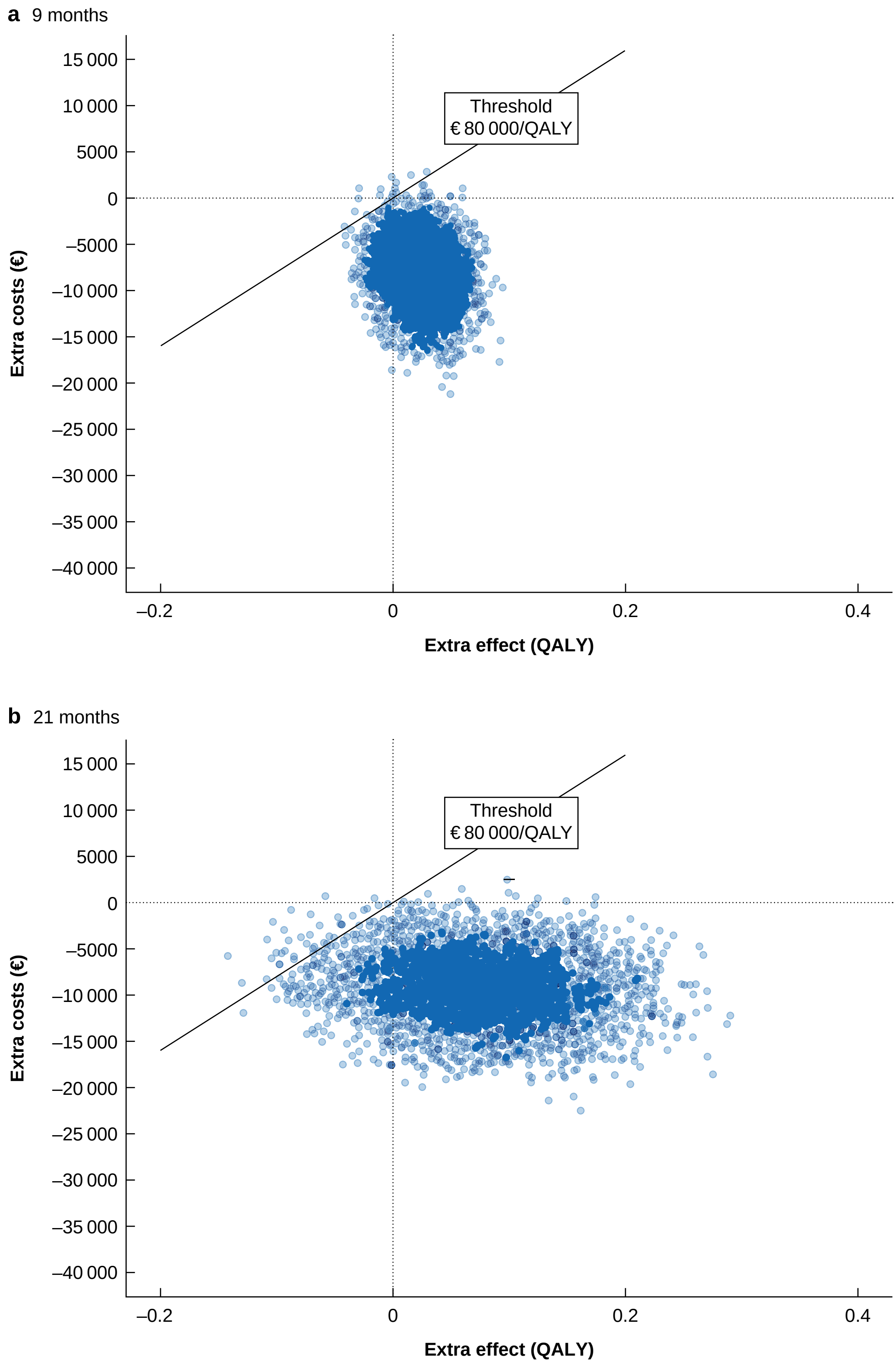

Fig. 1 Cost-effectiveness plane of incremental costs per quality-adjusted life-years gained for each of the bootstrap replications from a societal perspective at 9 and 21 months

a 9 months and **b** 21 months. QALY, quality-adjusted life-year; €, euros.

Discussion

This economic evaluation alongside the ICAN trial showed that MIE with intrathoracic anastomosis had similar QALYs after 9 and 21 months compared with MIE with cervical anastomosis. MIE with intrathoracic anastomosis was less costly than MIE with cervical anastomosis after 9 and 21 months of follow-up. This indicates that MIE with intrathoracic anastomosis surpasses MIE with cervical anastomosis from a cost-effectiveness standpoint.

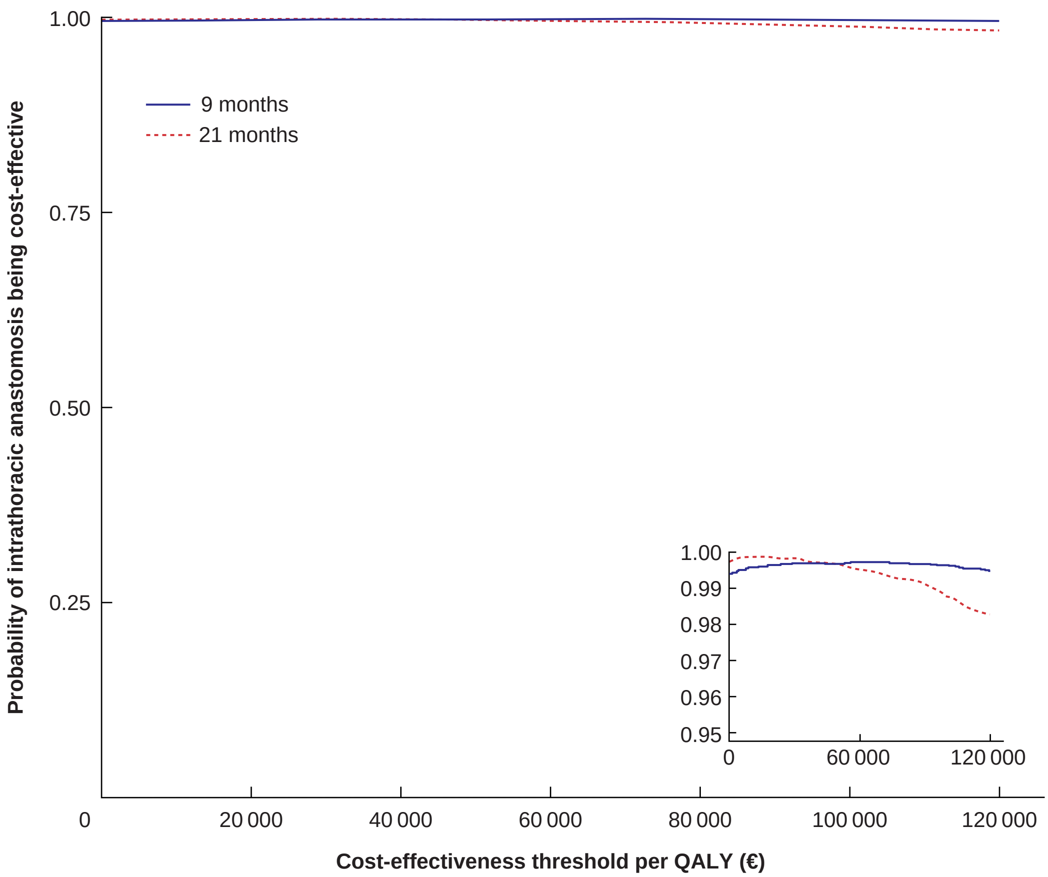

Fig. 2 Cost acceptability curves illustrating the probability that minimally invasive oesophagectomy with intrathoracic anastomosis is more cost-effective than minimally invasive oesophagectomy with cervical anastomosis, from a societal perspective at different cost-effectiveness thresholds

Insert shows magnification of the curves from 0.95 to 1.00 on the y-axis. €, euros.

To the authors' knowledge, this is the first economic evaluation of MIE with intrathoracic anastomosis *versus* MIE with cervical anastomosis. There are some published studies[28,29] comparing the cost-effectiveness of open oesophagectomy *versus* video-assisted thoracoscopic oesophagectomy. The first study, conducted in a Taiwanese population, showed overall 1-year costs of US$20 484, and overall cost after 24 months of US$23 861 in the video-assisted thoracoscopic oesophagectomy group. No specifications regarding the (abdominal) operation technique or anastomosis location were made. Costs were derived retrospectively from Taiwanese Health Insurance claim data. As an effect measure for the cost-effectiveness analysis, life-years were used instead of QALYs, and therefore no direct comparison with the present study can be made. The second study used a decision-analytical model to estimate the expected costs and outcomes of MIE and open oesophagectomy. The authors reported an estimated cost of 45 892 Canadian dollars and 0.623 QALYs for the MIE group compared with 47 533 Canadian dollars and 0.601 QALYs over 1 year. Owing the nature of the analysis, combined with the differences in healthcare costs between jurisdictions, no direct comparison with the present study can be made.

Some limitations also warrant discussion. First, this study showed that the cost difference between MIE with intrathoracic or cervical anastomosis is mainly due to the difference in hospital costs. The driving factor in this difference is, arguably, the difference in incidence of anastomotic leakage and other severe complications, which are associated with high treatment costs, longer hospital stay, and ICU readmission rates. The overall leak rate of 22% in the ICAN trial is slightly higher compared with a leak rate ranging from 18 to 20% documented in the annual reports of the Dutch Upper GI Cancer Audit (DUCA)[30] during the study period 2015–2019. However, the anastomotic leak rate of 34% in the cervical group stands out compared with the cervical anastomosis leak rates reported in other studies[10,31]. Other Dutch randomized clinical trials[32,33] also reported higher than average cervical anastomotic leak rates. A possible explanation is that an inclusive definition and meticulous data registration may have contributed to comprehensive and complete reporting of anastomotic leak rates[32,33]. Another potential explanation is that, in the Netherlands, the switch to MIE with intrathoracic anastomosis was made some years before the start of the ICAN trial and this could potentially have led to less experience with cervical anastomosis in some of the participating hospitals. A reduction in the cervical anastomosis leak rate will likely have influenced the cost-effectiveness analysis. However, even if the leak rate after cervical anastomosis were lower, MIE with intrathoracic anastomosis would be expected to remain cost-effective because intrathoracic anastomosis was also associated with fewer other severe postoperative complications (for example chyle leakage and empyema) with Clavien–Dindo grade ≥ IIIb: 5.7% in the intrathoracic anastomosis group *versus* 10.6% in the cervical anastomosis group[16].

Second, to reduce patient burden, the patient questionnaires regarding HRQoL and resource use were completed at 9 and

21 months after surgery instead of 12 and 24 months, as part of the ongoing POCOP registry. The 12- and the 24-month resource use from the CRF were used as a proxy for the 9- and 21-month costs. It was assumed that the in-hospital resource use was not substantially different between 9 and 12 months, and 21 and 24 months, respectively, after surgery. Actual resource use may have been slightly lower at 9 and 21 months, but this would not have changed the conclusion that MIE with intrathoracic anastomosis is less costly, with similar QALYs, and thus cost-effective.

Third, not all costs were included in the cost analysis, because costs common to both strategies need not be considered as they will not affect the choice between the strategies[22]. Costs for neoadjuvant treatment were not included because most patients received neoadjuvant treatment. Costs of treatment of recurrence and productivity costs were not included because the productivity loss and recurrence rates were similar between groups.

In this study, from a societal perspective, the mean costs per patient were €9931 less in patients with MIE with intrathoracic anastomosis compared with cervical anastomosis after 21 months. To calculate the possible economic impact of using MIE with intrathoracic anastomosis, the budget impact for 1 year was assessed. The authors took into account that, according to the DUCA annual report of 2022, in the Netherlands, approximately 95% of all oesophagectomies (770) are MIE, and 30% of all MIEs are MIE with cervical anastomosis. Switching 50% of all MIEs with cervical anastomosis to MIEs with intrathoracic anastomosis in the Netherlands would save approximately €1 000 000 annually without compromising HRQoL.

The ICAN trial showed statistically significant reductions in anastomotic leak rates and severe complications for transthoracic MIE with intrathoracic anastomosis compared with MIE with cervical anastomosis. It also showed a lower incidence of laryngeal nerve palsy and slightly better short-term quality of life. In light of these findings, a further shift towards MIE with intrathoracic anastomosis seems justified. However, for broader implementation of MIE with intrathoracic anastomosis, it should be noted that learning curves for MIE can be associated with significant morbidity, which has especially been shown for MIE with intrathoracic anastomosis. The learning curve for MIE with intrathoracic anastomosis ranges between 119 and 179 procedures, and a considerable number of patients experience learning-associated anastomotic leakage[34,35]. This could potentially result in an increase in costs during this learning curve. However, after a plateau has been reached, the reduction in costs in the intrathoracic group makes these potentially higher costs during the learning curve a worthwhile investment.

After analysis of the ICAN trial data, transthoracic MIE with intrathoracic anastomosis was found to surpass transthoracic MIE with cervical anastomosis and is thus deemed cost-effective.

Collaborators

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Funding

The Netherlands Organization for Health Research Development (ZonMw), grant 843002607, supported the ICAN trial financially.

Author contributions

Eric Matthée (Data curation, Formal analysis, Writing—original draft, Writing—review & editing), Sander Ubels (Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing—review & editing), Bastiaan Klarenbeek (Conceptualization, Funding acquisition, Methodology, Supervision, Writing—review & editing), Moniek H. P. Verstegen (Conceptualization, Data curation, Funding acquisition, Project administration, Writing—review & editing), Gerjon Hannink (Conceptualization, Methodology, Software, Supervision, Writing—review & editing), Frans T.W.E van Workum (Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Writing—review & editing), Camiel Rosman (Conceptualization, Data curation, Funding acquisition, Methodology, Supervision, Writing—review & editing), and Janneke P. C. Grutters (Formal analysis, Methodology, Supervision, Validation, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

Study data are available upon reasonable request.

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