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Original study

The impact of postoperative Patient-controlled epidural versus patient-controlled intravenous analgesia on cancer recurrence following minimally invasive esophagectomy: A retrospective analysis

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Abstract

Background: **Surgical resection, for the most part after neoadjuvant therapy, remains the primary curative option for esophageal cancer, yet cancer recurrence poses a significant challenge to patient outcomes. Previous literature has shown that various anesthetic drugs could potentially influence oncological outcomes after surgical resection of malignant tumors. This retrospective cohort study investigates the influence of patient-controlled epidural analgesia (PCEA) compared to patient-controlled intravenous analgesia (PCIA) on cancer recurrence following minimally invasive and hybrid esophagectomy.**

Methods: **A single center database analysis was conducted and 290 patients who underwent minimally invasive and hybrid esophagectomy between 2014 and 2020 were included in the analysis. Primary outcome was time to cancer recurrence. Time to death was considered a secondary outcome. A competing risk analysis was conducted using a cumulative incidence function.**

Results: **No statistical significant difference in recurrence-free survival time was found between patients with patient controlled epidural analgesia (PCEA) and patient controlled intravenous analgesia (PCIA) following esophagectomy, hazard ratio (HR) 1.08 with a 95% confidence interval (CI) of [0.63, 1.86]. For time to death no statistical significant difference could be found between PCEA and PCIA group following esophagectomy, HR of 0.87 with a 95% CI of [0.46, 1.64].**

Conclusion: **No statistical significant oncological or survival benefit could be found in patients treated with PCEA after minimally invasive esophagectomy. Despite the absence of statistical significant findings on cancer recurrence in this study, the well-established benefits of epidural analgesia in postoperative pain management and opioid reduction remain pertinent. Further research, particularly randomized controlled trials, is necessary to elucidate the potential impact of anesthesiologic techniques on oncological outcomes in esophageal cancer surgery.**

Keywords: **Oesophageal cancer, Esophagectomy, Epidural analgesia, Cancer recurrence.**

Authors' contributions A. De Norre.: Study design, literature study, ethics committee submission, data collection, data analysis, writing of manuscript. E. Van Daele, H. Vanommeslaeghe2, P. Pattyn: data collection, database management, proofreading manuscript. L. De Baerdemaeker: Study design, ethics committee submission, proofreading manuscript. P. Wyffels: Data analysis, proofreading manuscript.

This retrospective observational study was approved by the Ethics Committee of the Ghent University Hospital and Ghent University on 30 June 2022 (ref. THE-2022-0059).

Introduction

Esophageal cancer is currently the seventh most common cancer worldwide and responsible for about 450.000 deaths per year[1]. It comprises mainly squamous cell carcinoma (SCC) and esophageal adenocarcinoma (OAC). Survival rates approach a 5 year survival of 50%. Esophageal cancer presents as localized disease in approximately 22% of the cases, or regional advanced disease in approximately 30% of the cases[2]. The main therapeutic option in these cases is surgery, mostly preceded by neoadjuvant chemo- and or radiotherapy, and the intention is curative. Failure to prevent metastatic disease is responsible for approximately 90% of mortality in patients with cancer[1]. It is evident that cancer recurrence, metastatic or locally, of surgically removed tumors is a primary goal in treatment.

Development of cancer is a multistep process in which multiple conditions must be fulfilled for cancer to be able to develop, form metastasis and spread across the body. The six historical hallmarks necessary for cancer to develop are: resisting cell death, proliferative signaling, activating metastasis and invasion, resisting growth suppressing signaling, inducing angiogenesis and enabling replicative immortality[3]. More recently additional hallmarks have been identified as having an important role in tumor progression: promotion of inflammation, avoiding immune destruction, genome instability and dysregulation of cellular metabolism. The perioperative period is a critical period for the spreading and reactivation of cancer cells, as the surgical stress response and anesthetic manipulation alter the propagation of cancer cells and the immune response on top of spreading of cancer cell by direct manipulation of the tumor[4,5]. To mitigate the stress response, surgical techniques have become more minimally invasive[6] and of course effective anesthetic techniques seek to keep the stress response to a minimum.

In vitro and in vivo studies have confirmed that several anesthetics and adjuvant drugs used in anesthesia exhibit multiple effects on oncogenesis[5,7-9]. Pre-clinical studies have shown local anesthetics have numerous direct and indirect mechanisms which can reduce tumor progression. Concerning the effect of opioids on tumor progression there is conflicting evidence. Volatile anesthetics are associated with worse oncological outcomes when compared to the total intravenous anesthesia (TIVA) agent propofol[3].

We hypothesize that patients treated with patient controlled epidural analgesia (PCEA) experience improved disease-free survival time compared to those receiving patient controlled intravenous analgesia (PCIA) with morphine. This improvement is expected due to two primary mechanisms: 1) the anti-oncogenic effects of local anesthetics, and 2) the reduction of morphine consumption in PCEA patients, thereby limiting potential pro-oncogenic effects.

This study aims to investigate if there is an effect on cancer recurrence as primary outcome and overall survival as secondary outcome after minimally invasive esophagectomy for esophageal cancer. Patients receiving PCEA with local anesthetics will be retrospectively compared to patients PCIA with morphine.

In current literature few randomized controlled trials (RCTs) haven been conducted investigating the effect of local anesthetics on cancer recurrence after oncological surgery and retrospective studies have produced mixed results[3,10-16].

Materials and methods

This is a retrospective observational study approved by the Ethics Committee of the Ghent University Hospital and Ghent University on 30 June 2022 (ref. THE-2022-0059). Patients who underwent minimal invasive esophagectomy (MIE) or hybrid esophagectomy from February 2014 to September 2020 in the Ghent University Hospital were included. All patients had preoperatively given their written informed consent for data to be collected in a database managed by the department of gastro-intestinal surgery of the Ghent University Hospital to be used in future retrospective research.

Inclusion criteria are: 1. MIE or Hybrid esophagectomy for esophageal malignancy; 2. patient age 18 years or older; 3. R0 resection, defined as macroscopic complete removal of all tumoral lesions and microscopic tumor free edges of resected tissue; 4. PCEA or PCIA for postoperative pain control and 5. postoperative follow up concerning recurrence.

The investigated primary outcome is time to cancer recurrence. Recurrence was defined as CT graphic evidence of metastatic disease or local recurrence potentially confirmed by histological evidence of malignancy. As a secondary outcome overall survival is compared between the PCEA and PCIA group. This manuscript adheres to the applicable STROBE (Strengthening the reporting of observational studies in epidemiology) guidelines.

Anesthesia

All patient scheduled for elective esophagectomy received a pre anesthetic consultation by an

anesthesiologist, in which a preoperative workout was performed. The anesthetic plan was discussed with the patient, including potential placement of an epidural catheter prior to induction. Standard institutional protocol consisted of a balanced general anesthesia, in combination with thoracic epidural anesthesia. In case of either contra-indications for epidural placement, patient refusal or failed catheter insertion, no epidural anesthesia was employed and PCIA with morphine was applied. General anesthesia was induced with propofol in combination with sufentanil or remifentanil and rocuronium. Maintenance of anesthesia was done by either continuous propofol infusion or inhaled sevoflurane. Choice of opioid, and adjuvant drugs for maintenance of anesthesia were left at the discretion of the attending anesthesiologist. In those patients who received an epidural, a loading dose of 8-12ml ropivacaine 0.75% (7,5mg/ml) or 5-10ml levobupivacaine 0.5% (5mg/ml) was administered epidurally. Intraoperative top-up boluses were administered every 3-4h at 1/3 of the initial dose, or continuous infusion of ropivacaine 0,2% at a rate of 4ml/h was started after the initial loading dose.

Surgical procedure

All esophagectomies were performed by one of three experienced surgeons of the gastro-intestinal surgery department of the Ghent University Hospital. All esophagectomies where performed via an 'Ivor Lewis' procedure in minimally invasive or hybrid approach. MIE comprised a 2-staged surgical procedure consisting of a laparoscopy and thoracoscopy. The hybrid approach comprised a similar 2-staged approach in which either thoracoscopy or laparoscopy was not deemed feasible and either thoracotomy or laparotomy was performed. Complete resection of malignant lesions with tumor cell free margins and resection of lymph nodes was the goal of each procedure. The intent was curative as patients with metastatic disease prior to surgery were excluded.

Post-operative analgesia and follow up

All patients were admitted to the surgical intensive care unit (SICU) postoperatively. For patients with PCEA postoperative analgesia was provided with a mixture of 2mg/ml ropivacaine and 0,75mcg/ml sufentanil. PCEA was started as continuous infusion of 4ml/h with bolus of 4ml as needed. If needed, intravenous morphine was used as rescue drug for severe pain. In patients with PCIA postoperative pain was managed with a mixture of morphine 1mg/ml and droperidol 0.05mg/ml. PCIA was initiated as bolus only of 1ml every 8 minutes as needed. All patients received daily follow up by the acute postoperative pain team from the anesthetic department. PCA was typically continued for 2-5 days postoperatively. All patients received paracetamol as basic analgesic.

Oncological follow-up was performed in hospital by the gastro-intestinal surgery department of the Ghent University Hospital by CT-scan in 3-months interval the first two years, 6-month interval third year and yearly until a five year follow up period was completed. Earlier CT-scan was possible if relapse was suspected. Follow up in a referring center was possible by the same intervals if requested by the patient.

Statistical analysis

The primary endpoint of this study is time to cancer recurrence after surgery, defined as recurrence-free survival (RFS).

Prior to statistical analysis a sample size calculation was performed. We used a sample size calculation for a two-sided log-rank test, which is equivalent to the calculation for the proportional hazard Cox's regression[17]. A prior smaller retrospective study by Hiller et Al. showed a hazard ratio (HR) for cancer recurrence after gastro-intestinal surgery after two years of 0.33 in favor of epidural anesthesia[14] and a pilot study in our institution by Ochieng et al. showed a HR of 0.56[18]. Based on these results an expected hazard ration of 0.33 was utilized alongside a two-sided type 1 error rate of 0.05 (α) and a power of 80%. Calculated total events necessary was 51, considering the unequal sample sizes. Since the number of events (=cancer recurrence) was 106, we can conclude that sample size was adequate.

Descriptive statistical analysis on baseline characteristics was performed comparing the PCEA to PCIA group to identify potential confounders. Statistical significance was determined by employing Chi-square test for categorical variables and independent Students t-test or the non-parametric Wilcoxon rank sum test, when appropriate. Initially univariate Simple Kaplan Meier estimate and Cox proportional-hazard regression analysis was performed to investigate an association between time to cancer recurrence and the use of PCEA or PCIA. As several patients died before a diagnosis of cancer recurrence could be established, this was viewed as a competing event. To correct for this phenomenon a competing risk analysis using the cumulative incidence function as described by Fine and Grey was determined[19,20]. Subgroup analysis was performed focusing on surgical approach (hybrid vs MIE), tumor staging (clinical TMN-classification) and cachexia preoperatively (BMI <18), as these were determined by literature to have a potential

influence on the effect of PCEA or opioid on cancer recurrence[21]. These variables were included in a competing risk regression model for multivariate analysis.

Statistical significance for each test was defined as a p-value < 0.05. Results are reported with their 95% confidence intervals (CI). All statistical analyses were performed using statistical software R version 4.3.1 (The R Foundation, Vienna, Austria 2023) with packages: Tidyverse version: 2.0.0, Cmprsk version: 2.2-11 and Tidycmprsk version: 0.2.0.

Results

After application of the inclusion criteria 306 patients remained eligible. Of these patients, one was excluded for metastatic disease preoperatively and four for a non-malignant disease. Eight were excluded because of incomplete follow up data and two for missing data on PCEA or PCIA. Of the remaining 290 patients, 247 were categorized in the PCEA group and 43 in the PCIA group.

Baseline characteristics are summarized in Table I. Mean follow-up time was 882 days. There were no significant differences in baselin https://www.google.com/imgres?q=ster&imgurl=https%3A%2F%2Fstatic.vecteezy.com%2Fti%2Fgratis-vector%2Fp1%2F49947888-ster-vorm-symbool-zwart-en-wit-silhouet-illustratie-van-gemakkelijk-vijfpuntig-ster-geisoleerd-aan-wit-achtergrond-vector.jpg&imgrefurl=https%3A%2F%2Fnl.vecteezy.com%2Fvector-kunst%2F49947888-ster-vorm-symbool-zwart-en-wit-silhouet-illustratie-van-gemakkelijk-vijfpuntig-ster-geisoleerd-aan-wit-achtergrond&docid=HOblM8OIlkOtHM&tbnid=_yy2MW0soOaF1M&vet=12ahUKEwinspf_vb6LAxUDK_sDHbf9IdgQM3oECFoQAA..i&w=980&h=980&hcb=2&ved=2ahUKEwinspf_vb6LAxUDK_sDHbf9IdgQM3oECFoQAA e characteristics between the PCEA and PCIA group, except for surgical approach. In the PCEA group 64,4% of the patients underwent surgery with a MIE approach, compared to 44.2% in the PCIA group. As the approach differed between the two groups, this was included in the subgroup analysis to determine whether this has a significant effect on the primary outcome.

Primary Outcome: time to cancer recurrence

Median overall disease-free survival time, defined as days until relapse was detected, days until death or days until last follow up visit (whichever event occurred first), was 716 days, interquartile range 208 – 1359, for the PCEA group and 845 days, interquartile range 263 - 1245 for the PCIA group, which resulted in a non-statistically significant difference (p = 0.927).

Of the patients who died during the follow-up, 68 (44%) had died before a diagnosis of cancer recurrence could be established. At the end of data collection cancer recurrence was detected in 91 of 247 (36.8%) patients in the PCEA group and 15 of 43 (34.9%) patients in the PCIA group, a non-significant difference with a p-value of 0.941. Univariate Cumulative incidence analysis resulted in a non-significant HR of 1.08 for earlier cancer recurrence in the PCEA group. Results of the competing risk analysis for cancer time to cancer recurrence can be found in Table II and figure 2.

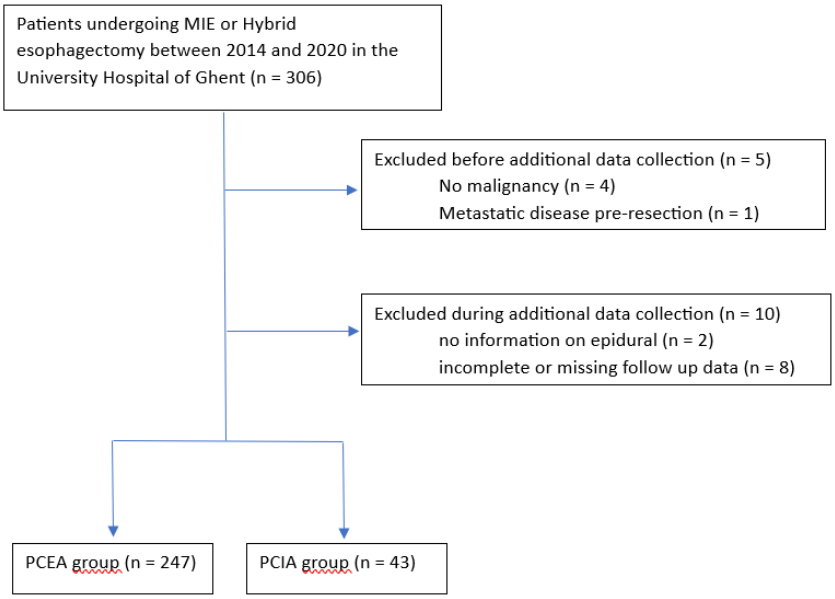

Fig. 1 — Flow diagram of selection process of patients included in this retrospective analysis.

Table I. — Patient characteristics.

Characteristics		PCIA (n = 43)	PCEA (n=247)	p-Value
Age		68.05 (8.90)	64.51 (13.12)	0.090
Male		35 (81.4)	199 (80.6)	1.000
BMI		26.53 (4.96)	25.58 (4.59)	0.220
ASA-classification	Missing	0 (0.0)	3 (1.2)	0.721
	1	3 (7.0)	11 (4.5)	
	2	17 (39.5)	110 (44.7)	
	3	23 (53.5)	122 (49.6)	
Smoker		11 (25.6)	83 (33.6)	0.389
Diabetes Mellitus		9 (20.9)	36(14.6)	0.404
Postoperative radiotherapy		0 (0)	6 (2.4)	0.659
	Missing	5 (11.6)	25 (10.1)	
Postoperative chemotherapy		2 (4.7)	30 (12.1)	0.245
	Missing	5 (11.6)	25 (10.1)	
Approach	Hybrid	24 (55.8)	88 (35.6)	0.019
	MIE	19 (44.2)	159 (64.4)	
Barret		13 (34.2)	78 (35.3)	1.000
N-classification	N0	12 (27.9)	79 (32.0)	0.854
	N1	18 (41.9)	107 (43.3)	
	N2	9 (20.9)	45 (18.2)	
	N3	4 (9.3)	16 (6.5)	

The data are means ± SD, N (%).
N, number of patients; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; BMI, body mass index; ASA, American Society of Anesthesiologists; MIE, minimally invasive esophagectomy; N-classification, lymph node-classification.

Table II. — Univariate cumulative incidence regression analysis for relapse, adjusted for competing risk of death.

Characteristic	N	HR	95% CI	p-value
PCIA	43	—	—	
PCEA	247	1.08	0.63, 1.86	0.8

N, number of patients; HR, Hazard ratio; CI, Confidence interval; PCIA, Patient controlled intravenous analgesia; PCEA, Patient controlled Epidural analgesia.

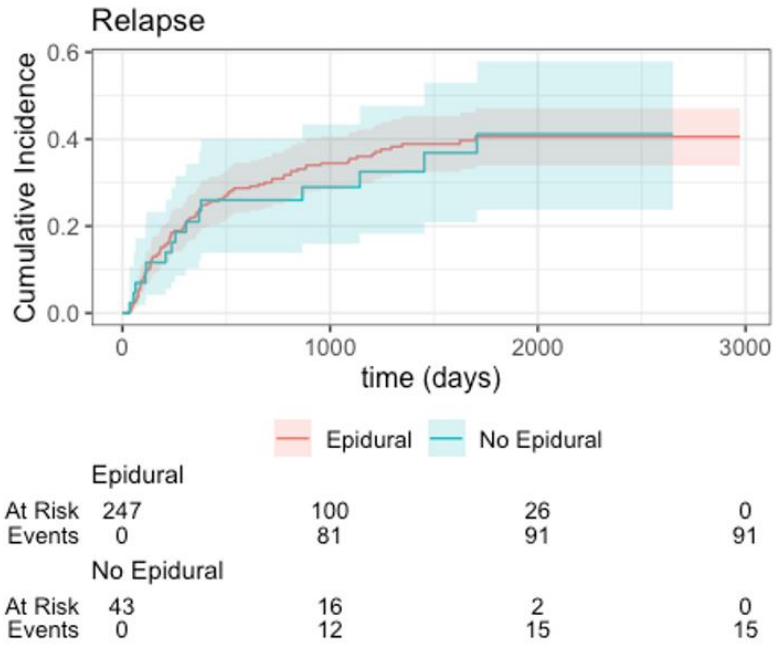

Fig. 2 — Cumulative incidence function of cancer recurrence after esophagectomy, adjusted for the competing risk of death. Colored boxes indicate 95% CI.

Secondary outcome: time to mortality

Overall, 127 (51.4%) patients had died in the PCEA group compared to 25 (58.1%) patients in the PCIA group, a non-significant difference with a p-value of 0.516. Univariate Cumulative incidence analysis resulted in a non-significant HR of 0.87 for earlier all-cause mortality in the PCEA group. Results of the competing risk analysis for time to all-cause mortality can be found in Table III and figure 3.

Subgroup analysis

To investigate the potential effect of confounding factors we conducted a competing risk regression analysis. We included tumor staging classification and preoperative presence of cachexia, defined as a BMI of <18, as these factors are shown in previous studies to significantly increase the risk for earlier recurrence of cancer. We also included the surgical approach as potential confounding factor as there was a significant difference between surgical techniques used in the PCEA and PCIA group, and as an approach which is associated with increased surgical stress could potentially increase the risk for recurrence.

The competing risk regression analysis showed no significant difference in time to relapse for any of the potential confounding factors, except for tumor staging, and more specifically a significant increased risk for patients with lymph node positive status at increased hazard ratio of 2.56, 95%CI (1.53, 4.16) ($p < 0.001$) compared to lymph node negative staging.

As lymph node status was a strong risk factor for early relapse, and a previous pilot study including patients undergoing esophagectomy suggested an increased benefit of epidural analgesia in relapse rates among patients with positive lymph node status[18], interaction of a positive lymph node status with the effect of PCEA or PCIA on time to cancer recurrence was additionally tested. This showed a marginal significant increased risk for relapse in the PCIA group when lymph node status was negative, HR 3.12, 95% CI (1.00, 9.70). But since there were only 12 patients in this specific subgroup and 95% confidence interval is very large, no meaningful conclusion can be made from this interaction term.

Table III. — Univariate cumulative incidence regression analysis for mortality.

Characteristic	N	HR	95% CI	p-value
PCIA	43	—	—	
PCEA	247	0.87	0.46, 1.64	0.7

N, number of patients; HR, Hazard ratio; CI, Confidence interval; PCIA, Patient controlled intravenous analgesia; PCEA, Patient controlled epidural analgesia.

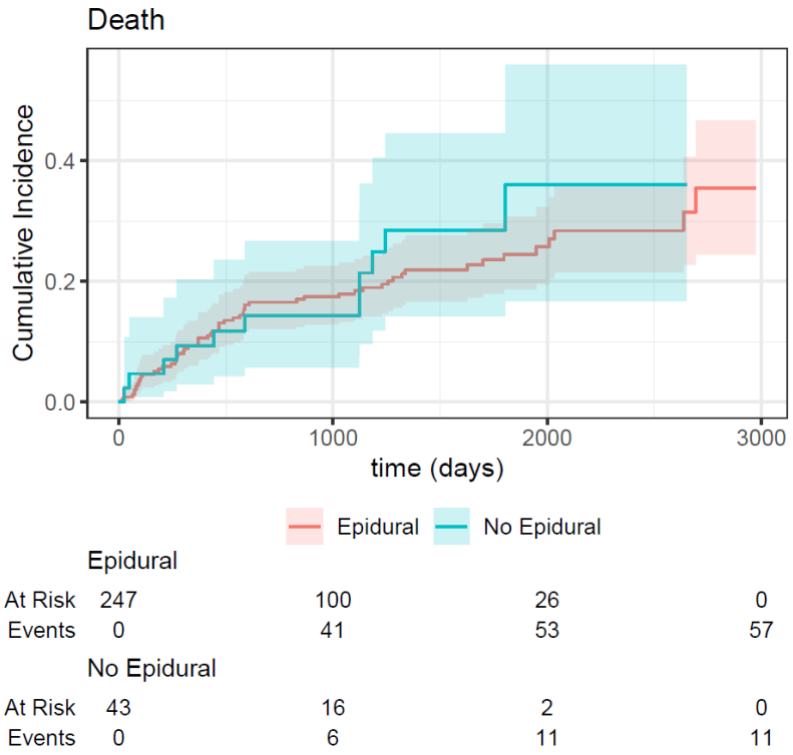

Fig. 3 — Cumulative incidence function of cancer recurrence after esophagectomy, adjusted for the competing risk of death. Colored boxes indicate 95% CI.

Characteristic	N	HR	95% CI	p-value
Tumor classification				
T1	36	—	—	
T2	57	1.78	0.76, 4.17	0.2
T3	190	1.39	0.61, 3.17	0.4
Node classification				
N+	199	—	—	
N0	91	0.39	0.24, 0.65	<0.001
Anesthetic technique				
PCEA	242	—	—	
PCIA	41	0.86	0.47, 1.55	0.6
Surgical approach				
Hybrid	108	—	—	
MIE	175	0.75	0.50, 1.13	0.2
BMI				
<18 (cachexia)	11	—	—	
>18	272	1.15	0.38, 3.45	0.8

N, number of patients; HR, hazard ratio; CI, confidence interval; PCIA, patient controlled intravenous analgesia; PCEA, patient controlled epidural analgesia; MIE, minimally invasive esophagectomy; BMI, body mass index.

Discussion

No significant reduction in time to local or metastatic recurrence of cancer could be found in our retrospective cohort study in patients who received PCEA after MIE or hybrid esophagectomy. These results are in line with the RCT's regarding the effect of local anesthetics on cancer recurrence after surgery for malignancy[11–13].

There is inconclusive evidence among the benefit on overall survival and cancer recurrence after surgery for malignant disease in patients who receive epidural analgesia (in combination with general anesthesia) intra-operatively and post-operatively. The heterogeneity of studies (malignancy type, stage and outcome endpoints) has produced inconsistent results. So far three retrospective studies looked at this outcome specifically after esophagectomy and found mixed results. One recent retrospective study by Hiller et al.[14], has suggested a positive effect on survival and recurrence, while other retrospective studies by Heinrich et al.[16] and Cummings III et al.[15] fail to show a significant effect. However, a survival or recurrence benefit could not yet be confirmed in recent randomized controlled trials[3,10]. To our best knowledge currently three RCT's have investigated a potential effect of local anesthesia techniques on cancer recurrence after surgical resection of other types of malignant tumors, which all have shown a non-significant difference compared to general anesthesia alone[11-13]. The largest retrospective cohort study by Cummings III et al. comprising 42,151 patients could not demonstrate a recurrence benefit for patient treated with epidural analgesia compared to traditional pain treatment after colectomy for colorectal canc[22].

Multivariate analysis has shown that a positive lymph node status is an independent risk factor for a decreased time to recurrence after esophagectomy (HR 2.56, 95% CI (1.53, 4.16)). A retrospective pilot study conducted in our center in 2011 by Ochieng et al. showed a Hazard Ratio with a 95% CI of 0.34 to 0.97 in time to recurrence favoring patients with PCEA compared to PCIA, but only in a subgroup of lymph node positive patients[18]. Lead by these results, we investigated if there was an interaction between lymph node status and PCEA/PCIA on time to cancer recurrence. This resulted in a large 95% CI for the HR (1.00, 9.70), which would indicate there is a lot of uncertainty about found HR. As such we did not consider this evidence of a relevant effect. A study with a larger population is warranted to investigate a potential interaction effect.

As with recurrence of malignant disease there is poor evidence of a mortality benefit for epidural analgesia in this setting. Retrospective analyses have both shown no evidence of statistical significant differences and statistical significant benefits for epidural anesthesia combined with general anesthesia versus general anesthesia alone concerning mortality[23] Currently no RCT's have shown a significant benefit for epidural analgesia[1,4]. We considered time to all-cause mortality as a secondary outcome and could not show a statistically significant difference between the PCEA group compared to the PCIA group.

As mentioned in the introduction many anesthetic drugs can influence oncological outcomes through numerous mechanisms[5,7-9]. Indirect effects of local anesthetics include diminished surgical stress response, immunomodulatory effects, reduced use of opioids and some anti-inflammatory effects. Direct effects are primarily mediated by effects on cell division and DNA-mediated effects[24,25]. Some of the in vitro studies on local anesthetics applied high concentrations exceeding the doses used in clinical anesthetic practice. Some studies however showed a positive effect with lower doses (> 10 µM) after longer exposure times >24hours[24]. As such the lower dosing of local anesthetics used in PCEA might still have relevant effects as PCEA systems stay in use for at least 2 days. There is conflicting evidence on the oncologic effects of opioids but overall evidence leans more towards a negative effect of opioids, mainly morphine, by suppressing cell mediated immunity, promoting cancer proliferation and angiogenesis. Synthetic opioids do not display these effects[3,26]. Agents used to maintain general anesthesia may also impact tumor progression. In vivo and in vitro studies have extensively compared total intravenous anesthetic agents, most commonly propofol, and inhaled anesthetic agents. In these studies, volatile anesthetics were associated with worse oncological outcomes[3]. Other adjunct medications commonly used in general anesthesia such as clonidine and ketamine have also shown oncologic mediating effects[3,27]. Still, the perioperative effects of anesthetics and surgery on the immune system, inflammation, stress response and direct effect on malignant cells is a complex multifactorial mechanism. That is why proving causality between anesthetics and cancer outcomes have proven to be difficult, mainly because these conditions are hard to mimic in in vitro environments.

As pre-clinical studies suggest an recurrence benefit of propofol based TIVA general anesthesia over volatile anesthetics clinical studies have provide mixed results. A large retrospective cohort study on long term oncological outcomes after breast conserving surgery for intraductal carcinoma showed a reduced hazard ratio (HR) for locoregional recurrence in patients who received propofol based TIVA general anesthesia compared to volatile based general anesthesia, no significant reduction of HR for distant metastasis could be demonstrated[28]. To date no RCT's have been completed investigating these effects[10].

Pre-clinical studies also suggest a potential adverse effect on oncological outcome of opioids. As such opioid free anesthesia (OFA) could potentially provide better oncological outcomes after oncological surgery. To date only one RCT has been conducted comparing biochemical recurrence after prostatectomy under OFA or opioid-based anesthesia, which could not demonstrate a significant benefit in the OFA group[29,30].

Minimally invasive surgical techniques are becoming a standard of care as they improve recovery after surgery and limit surgical stress response[6]. As stated above the perioperative period is a critical moment for possible metastatic disease progression. This study looked exclusively at MIE and hybrid surgical techniques, so the attenuation of the surgical stress response by using minimally invasive surgical techniques may be an important factor in limiting an effect of epidural analgesia on cancer recurrence. The results of this study show no evidence of a statistical significant impact on recurrence rate after MIE compared to the hybrid esophagectomy, but a larger effect could be expected when comparing MIE to an open surgical approach. A recent meta-analysis has identified seven observational studies comparing long term outcomes after MIE and open esophagectomy for esophageal cancer[31]. Although short term benefits on mortality and morbidity of MIE have been established, long term benefits on overall survival and cancer recurrence could not be demonstrated. Currently one RCT has compared long term effect of robotic assisted MIE compared to open surgical approach which could not demonstrate a statistical significant benefit on overall survival or disease free survival[32]. Regarding this evidence it is unclear whether surgical technique will have a significant influence on the effect of PCEA on cancer recurrence.

Even as no evidence of a statistical significant effect on time to cancer recurrence could be confirmed in this study, it is vital to underline the well-established advantages of epidural analgesia in oncological surgery. Epidural analgesia provides superior pain control and significantly reduces opioid consumption after surgery, thus mitigating negative effects opioid use, notably respiratory complications[33]. As such thoracic epidural analgesia is recommended as the first line approach by the enhanced recovery after surgery (ERAS) society guidelines for perioperative care in esophagectomy published in 2019, with moderate level of evidence and strong level of recommendation[34].

This study has several strengths. The analysis was conducted in a real life setting in an academic hospital which is a referral center for esophageal surgery in a large area with a high number of esophagectomies per year, with 87 esophagectomies in 2020. We used cumulative incidence function analysis to calculate differences in time to

recurrence between groups. Contrary to analyses used in previous studies on the effect of epidural analgesia on cancer recurrence, the cumulative incidence function analysis takes in to account the competing effect of death to the primary outcome, thus yielding a more accurate result. As shown in pre-clinical studies the contra-oncogenic effects of local anesthetics are more pronounced with longer exposure times, even when lower doses are used. In this study all patient in the PCEA group received intra- and postoperative epidural infusion of local anesthetics. Exact times of epidural infusions and cumulative doses are not reported, but all infusions exceeded a minimum duration of 24 hours. Lastly the surgical techniques employed in the study population represent the current approach towards surgery that is less invasive and as such is an essential part of enhanced recovery after surgery ERAS protocols for many types of surgeries.

There are limitations to this study. As this is a retrospective study, no randomization was performed. Epidural anesthesia combined with general anesthesia was first choice as anesthetic technique by center specific protocol. As a result, the PCIA group has a significantly smaller number of patients, 43 compared to 247, which makes it harder to achieve statistically significant results. The final decision of placing an epidural was led by any contra indications for epidural placement and was made by the attending anesthesiologist. No specific reason for the choice of PCEA or PCIA technique was recorded in our database. The duration of postoperative PCEA or PCIA treatment was led by patient reported pain scores, decision to continue or discontinue PCEA or PCEA was made each day by the acute postoperative pain team. As such there was no standardized duration of PCEA and PCIA therapy and treatment duration varied between 2 and 5 days between patients. As demonstrated in previous literature duration of exposure to local anesthetics might influence effects on oncological outcome[24]. As further subdivision of the groups for time of postoperative PCEA and PCIA treatment would yield groups with a small sample size statistical calculations would be underpowered and no meaningful conclusion could be made, this was not performed. Another consequence of this being a retrospective study is that there was no standardized induction and maintenance of general anesthesia. As discussed above, many anesthetic drugs have a potential effect on oncological outcome. Anesthetics used for maintenance of anesthesia, in particular volatile anesthetics or propofol based TIVA, were not recorded. As such maintenance of anesthesia could not be included in in the competing risk regression analysis. Opioids and morphine in particular express some pro-oncogenic effects. Cumulative opioid consumption for postoperative analgesia will very likely be reduced in the PCEA-group as extensive research has proven that epidural analgesia reduces opioid consumption in the perioperative phase for esophagectomy[35]. Data on cumulative opioid consumption could not be collected for this study, and as such the opioid sparing effect and the size of this effect could not be measured in this study.

Conclusion

No statistical significant benefit concerning time to cancer recurrence or mortality benefit after surgical resection through minimally invasive or hybrid surgical approach in patients treated with intraoperative epidural anesthesia and postoperative patient controlled epidural analgesia could be demonstrated in this study. Despite several theoretical effects to reduce spreading of malignant disease of epidural analgesia with local anesthetics, like reduction of opioid use, attenuation of surgical stress response and immunomodulatory and direct effect of local anesthetics, as of today, no randomized controlled trials were able to confirm the positive effect of epidural analgesia on cancer recurrence suggested by pre-clinical trials and retrospective analyses. To assess the real clinical effect of epidural analgesia on cancer recurrence after esophagectomy large RCT's are warranted.

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Data availability statement: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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