Review Article

Enhanced recovery after elective surgery for lung cancer patients: analysis of current pathways and perspectives

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Abstract: The concept of enhanced recovery after surgery (ERAS), initially introduced in the field of colorectal surgery, has been developed in order to optimize the postoperative course. In recent years the number of authors analyzing the role of ERAS in lung cancer surgery is increasing, highlighting several interventions with positive effects on the postoperative course. Yet it is still difficult to draw definite conclusions and specific guidelines, as most of these studies largely differ for their methodological aspects and study populations. Herein we focus on the key elements of each single intervention, trying to identify what we can apply in a common pathway, and which aspects are still to be evaluated for the validation of an ERAS program.

Keywords: Enhanced recovery; lung cancer; quality of life (QOL)

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Introduction

Lung cancer is the second most common malignancy in both men and women, with an annual incidence of 1.8 million new cases, and it is the leading cause of malignancies-related deaths in the developed countries (1). Lung cancer is also the main indication for thoracic surgery procedures, both for early stage disease and advanced disease in a multidisciplinary treatment approach.

Early detection of lung cancers and the novel targeted approaches, associated with the advances in surgical and anesthetic techniques, have brought to a larger number of surgical procedure and expanded the indications. However, the morbidity of elective lung surgery, at 30–40% as reported in literature, is still high (2). Post-operative complications are the most important cause of morbidity for thoracic surgical procedures, resulting in a prolonged hospital stay, delayed recovery, increased economic burden for the health care systems and ultimately a poor quality of life (QOL) for the patient (3,4).

The development of minimally invasive techniques has greatly reduced the incidence of peri-operative complications, making procedures acceptable also for patients otherwise considered at high risk.

In recent years physicians, and surgeons in particular, have focused their attention on specific in-hospital interventions with the goal of improving the post-operative course. However, it has become clear that these isolated interventions might not have a significant impact on outcome, whereas a multidisciplinary care plan is necessary, optimizing a variety of health care resources in the pre-, intra- and post-operative setting.

In this perspective, the concept of enhanced recovery after surgery (ERAS) has been developed. ERAS is a peri-operative multi-modal protocol of care, first introduced in the field of colorectal cancer surgery in the late 1990's and then applied also to other surgical fields (5).

The main purposes of ERAS protocols are to minimize the peri-operative stress response and catabolism with the ultimate goal of a faster post-operative recovery, shorter length of stay (LOS) and reduced morbidity. Unlike in fast-track protocols, in which the only aim is a shorter LOS, ERAS protocols combine multiple care elements in different phases (pre-, intra- and post-operative) in order to improve the patient's recovery (6). Therefore, we can say that ERAS is an augmentation of the fast-track approach.

While much of the evidence for ERAS is related to colorectal surgery, a recent meta-analysis of the literature, based on 38 randomized studies, demonstrated the efficacy of these type of interventions across all fields of surgery (7). As far as thoracic surgery is concerned, and particularly for the surgical treatment of non-small cell lung cancer (NSCLC), the data are limited regarding ERAS, and based on case series, non-randomized studies and a few randomized trials. Moreover, there is an important lack of information regarding the patients' expectations over the interventions associated with ERAS. Since at this time the data to draw definitive conclusions about ERAS in thoracic surgery is insufficient, but sure to grow in the future, it is important to track the early outcomes of ERAS experience.

Analysis of literature

The analysis of English-language medical literature showed a limited number of studies regarding ERAS in thoracic surgery. There are different case-report series showing good results of ERAS protocols, however the power of the evidence is very limited for the lack of a control group (8-10). Therefore, these studies represent a mere evaluation on the feasibility of a specific intervention, being impossible to evaluate the degree to which the outcomes are related to the intervention itself. On the other hand, different works, including also some randomized controlled trials, focus on the analysis of just one single aspect, such as pain control or chest drain management, not covering all phases of peri-operative care and thus being out of the definition of ERAS (11,12).

The studies treating the topic of ERAS, covering all peri- and intra-operative phases and with a control group are summarized in *Table S1* (3,13-24).

The most frequent type of studies are retrospective cohort studies (seven articles), followed by three prospective trials, two randomized controlled trials and a case control series. Indeed, these types of studies must be interpreted carefully since the majority of them are non-randomized, and thus are with increased risks of bias, particularly selection bias, that could favor the intervention group. On the other hand, randomized trials can overcome this potential confounding factor, but may be prone to other types of bias, particularly related to the non-blinded fashion of the trial. Analyzing the two randomized studies, in the case of Muehling and colleagues, the treatment allocation strategy and the randomization scheme were not described, and neither was any strategy to prevent detection bias (16). On the contrary, Dong and colleagues performed a block randomization, and in order to ensure double blinding, the evaluation of the patients' outcomes was performed by a researcher who did not know the procedures each patient was assigned to (21).

In terms of surgical approach and the extent of resections, there is much variety among the different studies. In the majority of the studies, the surgical approach is identical for the ERAS and the control group. However, in one study the surgical approach is not specified (17) and in four other works, the patients indifferently undergo minimally invasive or thoracotomy approach (3,18,23,24). In these last cases, generally there is no statistically significant difference in terms of surgical approach between the ERAS and standard-of-care groups, with the exception of the work of Numan and colleagues, where VATS approach is more frequent in the intervention group, being itself part of the ERAS protocol (18).

Moreover, only in the works by Van Haren and colleagues and Martin and colleagues a separate analysis between patients undergoing thoracotomy or VATS surgery has been performed and, interestingly enough, the decrease in LOS and complications was significant only for patients undergoing thoracotomy, whereas there were no differences for VATS patients (23,24). As in the other works such a separate analysis has not been performed, it remains unclear whether the positive effects of ERAS protocols are common for both subgroups or are relevant only for thoracotomy sub-groups, which however represent the majority of patients in these studies.

A lack of uniformity among the studies can be also found concerning the extent of surgical resection, with only five studies analyzing a single type of surgical procedure, either lobectomy (13,17,19,22) or pneumonectomy (21). In one case, the extent of resection is not specified (3), while in the other studies the surgical resection varies between wedge resections and pneumonectomies, nevertheless without showing statistical differences between control and intervention groups. No author performed an analysis between different subgroups in terms of extent of resection.

Table 1 Major peri- and intra-operative areas of intervention in ERAS protocols

Pre-operative	Intra-operative	Post-operative
Patient education	Warming of the patient	Early mobilization
Avoidance of prolonged fasting	Thoracic epidural anesthesia	Early feeding
	"Balanced" fluid regimen	Early removal of urinary catheter
	Minimally invasive approach	Standardized chest tube removal criteria

ERAS, enhanced recovery after surgery.

Areas of intervention

ERAS elements and areas of intervention largely vary across the different studies as there is not a standardized and internationally-accepted protocol of intervention. As shown in *Table 1*, major interventions may be divided in pre-, intra- and post-operative.

The mainstay of the ERAS pre-operative management is patient education. It is reported in each protocol and is described as standard and comprehensive, mostly through information provided in booklets. Another common step of the preoperative management, reported by six studies, is to avoid prolonged fasting by supplying clear liquids or glucose until 2 hours before surgery (16,20-24). Abbreviation of fasting, especially in patients affected by neoplastic disease, contributes to reduce the postoperative metabolic stress triggered by the tissue damage, and reduces the insulin resistance. Indeed, the muscle loss and the glycemic disorders are important prognostic factors to be observed in the postoperative period (25-27). Other interventions described in two or less studies are preventive analgesia, health assessment and improvement through respiratory exercises.

Regarding intra-operative interventions, warming of the patient and the use of thoracic epidural anesthesia (TEA) are most commonly described (14-16,18). While various regional analgesic techniques have been shown to be effective, as intercostal nerve block or local surgical infiltration, TEA is considered the "gold standard" for postoperative pain control in thoracic surgery (28,29). Its valuable efficacy in the postoperative period allows a massive reduction in opioid consumption, whose side effects are often responsible for delayed mobilization (30). Another common practice in anesthesia is restrictive fluid management. Despite the use of a restrictive intravenous fluid therapy showing a reduction in the postoperative complications in several large studies and meta-analysis in colorectal surgery (31-34), its influence in thoracic surgery has yet to be evaluated. More commonly, excessive fluid can lead to lung edema and the delayed mobilization of the patient. It also can contribute to the occurrence of other complications as atrial fibrillation. Based on these considerations, the fluid regimen in the ERAS protocol is correctly denominated as "balanced".

Among all kinds of interventions, certainly the extension of the resection and the surgical approach are the most important aspects capable of influencing the course of the patients during their postoperative period. According to the literature, a minimally invasive approach represents today the gold standard in thoracic surgery due to the reduction of post-operative pain and LOS, whilst maintaining the oncological efficacy (35-37). The common post-operative practices aimed to an early mobilization of the patient include early feeding, early removal of urinary catheter and standardized chest tube removal criteria (3,14-24). Even if these practices were already used in the common postoperative management, the ERAS protocol has led to a better standardized management, thus reducing the interobserver variability.

Outcome measures analysis

The main outcome measures used to evaluate the efficacy of ERAS protocols among the different studies are the LOS, complication rates, readmission rates and costs.

LOS

LOS is the most frequently evaluated parameter in all studies. When analyzing the two randomized trials there is a discrepancy in the results, with the work of Muehling and colleagues showing no differences in LOS (16,21). On the contrary, all but one of the non-randomized studies showed a reduction of post-operative LOS in the intervention group (13-15,17-19,22-24). As previously noticed, in the works by Martin *et al.* and Van Haren *et al.* this reduction was observed only in the thoracotomy group and not in the patients undergoing VATS, as if the intervention was more effective on thoracotomy than VATS (23,24). Moreover, this reduction in LOS is frequently associated with an early chest tube removal protocol or usage of electronic drainage systems (3,17-19,23,24). Indeed, a standardized chest tube management, with particular attention on defining a cut-off in effluent output for tube removal, and the use of an electronic device, with the advantages of a continuous monitoring for air leakage and a reduction in the inter-observer variability, have demonstrated a reduction in LOS among different studies outside an ERAS protocol (38).

Cost analysis

Strictly related to hospital LOS is the cost analysis. Indeed, hospital costs are mainly related to the days of hospital stay, with a reduction of the latter having a major impact on health care economy. Only three studies compare costs within an ERAS protocol, with all works showing a reduction in hospitalization costs concurrently with the reduction of hospital LOS (3,15,23). Paci and colleagues evaluated not only the in-hospital costs but expanded the analysis also to post-discharge socioeconomic costs, including health care system usage and caregiver burden. Post-discharge costs and indirect costs of the operation that can be defined as the lack of productivity due to the disease, which can affect the patients but also their relatives, are important indicators of recovery and are strictly related to the patients' QOL (3,39).

Complication rates

Complications rates are evaluated by all studies except for the one of Maruyama (3,13,14,16-24). However just four studies, included one randomized controlled trial, showed a reduction of complications in the ERAS groups, particularly pulmonary and cardiac morbidity (3,16,19,24).

Readmission rates

Eight studies analyzed readmission rates after surgery (3,13,17-21,23), but only Numan and colleagues found a statistically significant differences among the two groups (P=0.015) (18).

Patients perceived outcomes

QOL is defined by the World Health Organization as "individuals" perceptions of their position in life in the context of their culture and value systems in which they live and in relation to their goals, expectations, standards and concerns, thus a multidimensional concept incorporating all imaginable aspects that have impact on a person's life (40). Particularly in modern health-care systems the patients' perspective has gained attention, emerging as a fundamental point in the surgical decision making process and this aspect can be further emphasized in lung cancer patients, where diagnosis has tremendous effects on the physical and emotional spheres (4).

Surgical decision-making process is performed, in its simplest form, by analyzing the benefits and risks of each procedure and favoring the option where the benefit outweighs the risk. While benefits are easily recognized, the difficulties arise when trying to establish the size of risks (41). Although QOL is becoming one of the main endpoints in surgical literature, only Numan and colleagues analyzed this element related to ERAS protocols through a short-form health survey SF-36 administered pre-operatively and 1, 3 and 6 months after surgery. Patients treated in the ERAS protocol showed a trend towards improvement in physical QOL at 1 month (P=0.03) and at 6 months (P=0.07) after operation (18). Interestingly, this improvement in QOL was associated with a reduction of the LOS and of perceived pain, but not with a significant difference in the complications rate, showing that a better general management of the patients influences the perceived QOL much more than the general complications rate. This confirms also that outcomes measures that are evaluated by the physicians may not be the same as that which the patient is concerned mostly (4). Simple and direct measures of surgical risks are mortality and morbidity, and represent the most important endpoints in innumerable studies, such as hospital LOS, hospital readmission, and reoperation rates. However, the impact of the disease or of the treatment on the physical and psychological dimension of the patient must be also taken in consideration. Cykert and colleagues evaluated patients' preferences regarding possible outcomes of lung resection by evaluating general postoperative complications, prolonged debility (ventilator or oxygen dependence) or permanent incapacitation (need of assistance with activities of daily living, permanent ventilator dependency). It emerged that patients would not refuse surgery due to common post-operative complications (pneumonia, myocardial infarction), but are concerned equally about permanent disability and the possibility for lung cancer progression (42). Another study showed that among patients requiring surgery, the percentage desiring to be treated decreased as the probability of adverse outcome increased, but interestingly the reductions were bigger when the adverse outcome was disability rather than death (43). Thus, patients want to be cured but concurrently want to avoid any treatment that would cause a permanent disability, and all these aspects concur in the definition of QOL.

Discussion

There are different inherent difficulties when evaluating studies that deal with ERAS protocols that makes it like comparing proverbial apples to oranges and to many other fruits. Consequently, as described also by Fiore and colleagues, there is currently a lack of data to draw definitive conclusions on ERAS in thoracic surgery (44). The different approaches and areas of intervention of each study have been on major reason for absence of uniform and universally accepted conclusions. Indeed, we focused on studies covering all aspects of ERAS, however there are no specific guidelines for enhanced recovery in thoracic surgery and consequently interventions in the different peri-operative areas vary widely among the published studies. Moreover, it is difficult to evaluate the weight of each single intervention on the final outcome as many of the elements in the ERAS protocols, taken individually, have shown positive effects on the patient's outcome. Only in the work by Madani and colleagues an association between early chest drain removal and urinary catheter removal is shorter LOS found (19). While it appears that the whole pathway most likely is more important than any single intervention, adherence to the ERAS protocol also has been shown to be related to improved clinical outcomes as recently pointed out in a study by Rogers and colleagues. Surprisingly, this aspect has not been evaluated in any of the analyzed studies (45).

Another aspect that must be taken in consideration is the degree of difference between the interventional group and the group undergoing the previous standard-of-care at the institutional level. This is a factor that varies substantially from one center to another and, in some circumstances, if there is an insufficient difference, an observed lack of benefits conferred by ERAS may be found (20).

Third, the studies largely differ for their methodological aspects, thus resulting in different quality of evidence among the presented results. As stated earlier, non-randomized trials are prone to different types of bias, particularly a selection bias by the surgeons.

Finally, the heterogeneity of the study populations makes the comparison as well as the analysis of the results, fairly complicated. Indeed, as aforementioned, only a few studies focus their attention on a homogeneous population, in terms of surgical approach and extent of resection, whereas others describe a wider array of cases including open pneumonectomy mixed together with VATS wedge resection (23). This type of heterogeneity renders it difficult to evaluate the effect of the intervention over the influence of the type of operation itself. Undoubtedly, the introduction of VATS is the most important element of ERAS and it has resulted in considerable improvements in terms of peri-operative benefits, reducing incision-related pain, and thus, complications. As a consequence, the interventions other than the minimally invasive surgical approach have difficulty in demonstrating their beneficial effects in VATS patients, whereas they seem to determine significant better outcomes in patients undergoing thoracotomy (23,24).

There are two major pathways that should be implemented to facilitate the goal of ERAS (46). The first goal should address pain control strategies through overcoming the paradigm of epidural analgesia and focusing on paravertebral blockade and non-narcotic drugs. The second goal should focus on better chest tube management by reducing the subjective influence of the single surgeon and reducing inter-observer variability. Reducing subjective influences may be achieved through using strict protocols of chest tube management, particularly in terms of defining a fluid output threshold for its removal. Regarding the reducing inter-observer variability, the main problem is related to air leak assessment. Use of digital drainage systems have shown the capability of reducing the inter-observer variability and providing a more complete evaluation through the continuous monitoring (47), and thus, should be considered.

Finally, one important aspect that has been underestimated until now is the patients' perspectives on ERAS. Indeed, in the current era of medicine, this perspective is considered an essential element in the evaluation of clinical and surgical outcomes. Strangely it has been evaluated in just one trial (18). Patients' satisfaction often goes beyond the typical medical parameters that are used for the evaluation of outcomes by clinicians, such as morbidity and mortality and reflect more a general overview of management as perceived by the individual patient. For this important reason, holistic program such as ERAS cannot disregard the patients' subjective evaluation and as it is predictable that the results from pursuing this assessment will demonstrate significantly better outcomes in terms of QOL compared to control groups.

Conclusions

Current available data on ERAS pathways in thoracic surgery show encouraging results, however the weakness of their statistical power makes it difficult to draw definitive conclusions, and a standardized pathway has yet to be designed. Further studies with enhanced statistical power are necessary to prove conclusive evidences. Patients' perspectives have been little considered in the various studies until now. However, as it represents a major outcome measure in current clinical practices, it should be necessarily taken into account for the validation of an ERAS program.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Studies regarding ERAS in thoracic surgery covering all phases of perioperative care and providing a control group

Study	Design	Sample size		Surgical procedures		Operative approaches (VATS/open)		Interventions			Evidences
		ERAS	Control	ERAS	Control	ERAS	Control	Pre-operative	Intra-operative	Post-operative	
Wright, 1997 (13)	Retrospective cohort	130	147	LB 130	LB 147	0/130	0/147	Patient counseling	–	Standardized chest tube management; early removal of epidural catheter; nausea protocol	Reduced LOS and costs
Zehr, 1998 (14)	Prospective cohort	241	185	ST 83; LB 154; PN 4	ST 142; LB 36; PN 7	0/241	0/185	–	Early extubation; epidural analgesia	Standardized chest tube management; early mobilization and feeding; early O_2 weaning	Reduced LOS and costs
Maruyama, 2006 (15)	Retrospective cohort	113	105	LB 56%; ST+WR 41%; BL+PN 3%	LB 55%; ST+WR 44%; BL+PN 1%	113/0	105/0	Patient education; prophylactic antibiotics	Epidural analgesia	Early feeding (POD 1); early ambulation (POD 1); prevent fluid overload	Reduced duration of chest tube, LOS and costs
Muehling, 2008 (16)	Randomized controlled trial	30	28	LB/BL 20; PN 3; WR/SR 7	LB/BL 20; PN 1; WR/SR 7	0/30	0/28	Patient education; no prolonged fasting (clear liquid until 2 h before)	Intraoperative warming; Pain control with epidural analgesia + NSAID	Early feeding (evening of POD 0); early ambulation (evening of POD 0); prevent fluid overload (<1,000 mL/24 h)	Reduced of pulmonary complications rate
Salati, 2012 (17)	Case-control	232	232	LB 232	LB 232	–	–	Patient counseling	Fissureless lobectomy; single chest tube	Early chest tube removal; electronic drainage system; patient counseling	Reduced LOS
Numan, 2012 (18)	Prospective cohort	75	94	LB+ST45%; WR 41%; Other 14%	LB+ST 45%; WR 40%; other 15%	25/50	15/79	Patient counseling	Muscle sparing technique; Epidural anesthesia	Early mobilization/physiotherapy; standardized chest tube management; early removal of epidural catheter and rapid pain management	Reduced LOS, readmission rate and pain, better quality of life
Madani, 2015 (19)	Retrospective cohort	107	127	LB 107	LB 127	0/107	0/127	Patient education	Extubation in the operative room	Early removal urinary catheter; early chest tube removal; early feeding; early mobilization; target discharge	Reduced LOS and complications
Brunelli, 2017 (20)	Retrospective cohort	235	265	LB (?); ST (?)	LB (?); ST (?)	235/0*	265/0*	Patient education; preoperative health assessment; carbohydrate loading; preoperative warming; no prolonged fasting; same-day admission	Intraoperative warming	Postoperative discharge when criteria met; early mobilization; early feeding; nausea and vomiting prevention; prevent fluid overload; minimal use of systemic opioids	No benefit conferred by ERAS program
Dong, 2017 (21)	Randomized controlled trial	17	18	PN 17	PN 18	0/17	0/18	Patient education; no prolonged fasting (1,000 mL of 10% glucose orally at the night before operation and 200 mL 2 h before)	Intraoperative warming	Addition of nonsteroidal analgesic painkillers for 48 h; addition of fast intravenous infusion of 250 mL saline within 1 h p.o.; 400 mL liquid food 6 h p.o.; early extubation of urinary catheter (12 h p.o.); chewing gum to promote bowel movements; active bed activities of the lower limbs	Reduced LOS
Paci, 2017 (3)	Prospective cohort	75	58	–	–	24/51	16/42	Patient education	Extubation in the OR	Early oral intake (clear fluid diet POD 0, diet as tolerated POD 1); up to chair POD 0; up to chair 3 timed and ambulate 2 times POD 1; out of bed >8 h during the day and walking 17–35 m 3 times in POD 2; standardized chest tube removal criteria	Decreased hospital costs; reduced of pulmonary and overall complications rate; reduced LOS, lower costs
Huang, 2018 (22)	Retrospective cohort	38	45	LB 38	LB 45	38/0	45/0	Patient education; ceasing smoking and drinking; respiratory function exercises; blood pressure and blood sugar control; no prolonged fasting (500 mL of 10% glucose orally at the night before operation and 200 mL 2 h before)	Uniportal VATS Intraoperative warming; Avoiding of muscle relaxants; light anesthesia; addition of local anesthesia and intercostal nerve block	Addition of NSAID; nausea and vomiting prevention; prevent fluid overload (<500 mL/24 h); 1 h of activity out of bed within 24 h p.o. after which 4 h of activity out of bed every day; early extubation of urinary catheter	Better VAS on the third postoperative day; shorter chest tube placement duration; Reduced LOS
Martin, 2018 (23)	Retrospective cohort	139	224	SLB 62; LB 45; BL 3; PN 5; other 24	SLB 95; LB 74; BL 6; PN 6; other 43	81/58	162/62	Patient education; no prolonged fasting (Gatorade 20 oz. 2 h before operation); medications given orally in preoperative unit: gabapentin 600 mg; celecoxib 200 mg; acetaminophen 975 mg	Subarachnoid morphine; no intraoperative opioids; restrictive fluid management; surgeon-administered PINB	Diet: advance as tolerated; up to chair POD 0; out of bed at least 3 times daily; water seal as soon as possible	Reduced LOS only for thoracotomy; decreased opioids use; decreased hospital costs
Van Haren, 2018 (24)	Retrospective cohort	342	1,615	WR 17.5%; ST 9.4%; LB 64.3%; SLB 4.1%; BL 5.8%; PN 5.6%	WR 14.7%; ST 7.7%; LB 70.7%; SLB 5%; BL 3.7%; PN 5.6%	VATS 40.3%; RAST 11.1%; THOR 49.6%	VATS 31.7%; RAST 0.9%; THOR 67.4%	Patient education; no prolonged fasting (clear liquid until 2 h before); preventive analgesia (tramadol 300 mg + gabapentin 300 mg)	Perioperative steroids; opioid-sparing analgesia; total i.v. anesthesia; regional anesthesia; fluid replacement guided according to a validated algorithm	Opioid-sparing analgesia; early ambulation; early oral intake (clear fluid diet POD 0; diet as tolerated POD 1); typically 1 chest tube placement	Reduced LOS, ICU readmission, and pulmonary and cardiac morbidity only after thoracotomy

*, it is unclear whether the 67 conversions from VATS to open are counted in the ERAS or in the control group. WR, wedge resection; ST, segmentectomy; LB, lobectomy; SLB, sleeve lobectomy; BL, bilobectomy; PN, pneumonectomy; VATS, video-assisted thoracoscopic surgery; ERAS, enhanced recovery after surgery; RATS, robotic-assisted thoracoscopic surgery; THOR, thoracotomy; POD, post-operative day; LOS, length of stay; OR, operating room; ICU, intensive care unit; PINB, posterior intercostal nerve block; NSAID, nonsteroidal anti-inflammatory drug; VAS, visual analogue scale.