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CLINICAL IMPACT OF SPINAL/EPIDURAL ANESTHESIA IN PATIENTS WHO UNDERGO MAJOR PELVIC SURGERY FOR CANCER

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Index

INTRODUCTION

Over the past decade, the scientific community has shifted its focus towards less invasive surgical and anesthesiological techniques for treating malignancies.
This has been made possible by the advancements in reliable and precise instrumentation, as well as the availability of more manageable drugs that minimize complications.
The rise in life expectancy and average age, along with an increase in cancer cases, has led to more elderly patients undergoing major surgeries despite their high comorbidities. As a result, the anesthesiological world has adapted by increasingly using locoregional anesthesia techniques for medium- and high-complexity abdominal surgeries instead of general anesthesia. These techniques help to limit perioperative risks, particularly intra- and postoperative cardiorespiratory complications, and reduce the need for intensive care unit access for these delicate patients.
It has been observed that using the combined spinoperidural technique (SpEA) in patients undergoing radical cystectomy can significantly improve outcomes for patients with ASA risk greater than 3. This is due to improvements in surgical techniques, anesthesia, and peri- and postoperative management, which have led to a reduction in complications and mortality rates associated with these procedures.
In bladder cancer, radical cystectomy (RC) is indicated for muscle-invasive bladder tumors (MIBCs) and multiple, recurrent, symptomatic, high-grade superficial tumors that cannot be treated endoscopically. The surgical technique not only provides adequate control of the disease in terms of oncological appearance but also serves as a highly effective treatment for complications related to bladder cancer, such as intractable hematuria or urinary tract obstruction.
Bladder cancer complications and various forms of palliative care, such as radiotherapy, often cause severe inconvenience to patients due to a significant deterioration in their quality of life. Radical cystectomy, although still associated with a complication rate of about 27% and a mortality rate of 0.8%, [1] remains an effective option for treating bladder cancer complications.
According to a previous report, the use of RC in patients over the age of 80 was linked to a mortality rate of 4.8% [2].

Recently, there has been an increased focus on locoregional techniques, particularly in patients with high cardio-respiratory comorbidities, due to the growing use of laparoscopic techniques [3]

Postoperative protocols suggest that laparoscopy offers better patient comfort and quicker recovery [4]

However, during laparoscopy, changes in hemodynamics and respiratory mechanics can be caused by the induction of pneumoperitoneum, mechanical ventilation, and surgical position [5] [6]

Some patients with cardiovascular or respiratory diseases may be less tolerant to these changes. This can pose a challenge for both the anesthesiologist and the surgeon due to the associated changes in heart-lung physiology and possible difficulties during the surgical procedure, awakening, and/or the postoperative period. However, new frontiers in surgery and anesthesia have opened up the possibility of using locoregional anesthesia to perform the same surgical procedures on these types of patients [7]

BLADDER CANCER

Bladder cancer is the second most common cancer of urological interest, following prostate adenocarcinoma. It is more prevalent among men than women, and most commonly affects people aged between 60 and 70. In Italy, about 25,500 new cases of bladder cancer were recorded in 2020, with 20,500 men and 5,000 women affected. This accounted for 10.5% and 3% of all new cancer cases for men and women, respectively [8]

In 2020, there were 6,253 deaths from bladder cancer, with 4,863 men and 1,390 women affected. While the mortality rate for men increased by 2.6% compared to 2015, it decreased by 2.6% for women. The 5-year survival rate is 79%, with no significant differences between men and women (80% for men and 78% for women). However, the survival rate decreases with age, from 96% for patients under 45 years to 66% for those over 75 [9]

About 90% of bladder cancers are transitional cell carcinomas (urothelial carcinomas) that arise from the cells lining the inner surface of the bladder. The remaining 10% of bladder tumors are primarily squamous cell carcinomas and adenocarcinomas. There are few other histologic types.

Cigarette smoking is the most significant risk factor, accounting for 50% of bladder cancer cases [10].

Other risk factors include:

- Exposure to radiation, following radiotherapy treatment of the pelvic region [11]

- Exposure to chemicals such as arsenic and products used in the rubber, leather, paint, and textile industries [12]

- Diet also plays a role: alcohol and fat consumed in large amounts are associated with increased risk [13]

Diagnosis may occur during a routine physical examination or be suspected by the presence of symptoms, such as:

- hematuria: generally not accompanied by pain, occurs in 85% of patients with bladder cancer.

- Irritative-type symptoms: urinary urgency, pollakiuria, stranguria.

Along with symptomatology, first-level investigations, such as ultrasonography and urine cytology, or second-level investigations, such as cystoscopy, are associated for diagnosis. CT, PET, and bone scintigraphy are second-level investigations for staging the same, indicated to assess the extent and possible involvement of other organs and thus the patient's prognosis [13]

Bladder tumors are classified by tumor stage, subtype, and degree of aggressiveness of tumor cells.

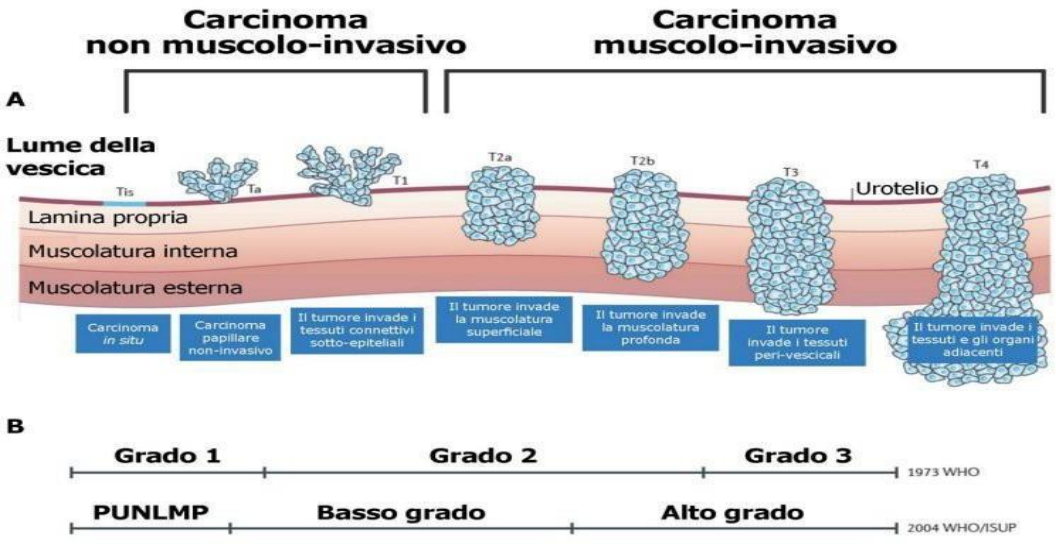
Staging is a standard way to describe the extent of a tumor's spread, and the commonly used staging method is the TNM system,

T (tumor size and invasion of surrounding tissues),

N (lymph node involvement),

M (presence of metastasis or tumor spread to other organs) [14].

<u>The diagram below shows the different stages of bladder cancer:</u>



The tumor stage indicates whether or not the tumor has invaded the bladder wall, which is essential information for identifying possible adjuvant treatments and the risk profile of recurrence or worsening.

Ta, T1 stages indicate a noninvasive tumor (Figure 1).

- Type Ta tumors are confined to the lining of the bladder and indicated as "mucosa"

- Type T1 tumors have invaded adjacent tissues beneath the bladder lining, but have not yet developed into the muscle of the bladder wall

Stages T2, T3, T4 indicate MUSCLE INVASIVE type cancer (MIBC) and have already developed tumors beyond the bladder mucosa.

The treatment will be different depending on the type of tumor:

NON-MUSCOLO-INVASIVE Bladder Carcinoma (NMIBC) is a neoplasm that has not infiltrated the detrusor muscle and accounts for about 70% of diagnosed bladder neoplasms. Most of these lesions are low-grade, but recurrence is common, especially ifmultiple lesions are present, and occurs in 50% to 70% of cases; progression occurs in 5% of cases [14].

There are various therapeutic options available for treatment, some of which can be used in combination with each other. One such option is:

TURB, which involves the use of a video-endoscopic technique to perform trans-urethral resection of the lesion. During the procedure, a resector is inserted into the bladder through the urethra.

The purpose of this procedure is to remove any visible bladder tumor and sample any suspicious areas for biopsy. Typically, a deep resection is performed to remove a part of the detrusor muscle as well [15].

A Repeat TURB, or Re-TURB, is recommended for the evaluation of high-grade T1 or Ta tumors diagnosed during the first TURB. It should also be considered when the initial resection is incomplete, such as in cases of multiple or large tumors, or when muscle tissue was not harvested during the first TURB [16].

Immunotherapy with BCG, which is an attenuated form of Mycobacterium bovis developed as a vaccine for tuberculosis, has demonstrated anti-tumor activity in several malignancies. Treatment with BCG typically begins 2 to 4 weeks after TURB, after the

lesions have re-epithelialized, to reduce the risk of dissemination of live bacteria [17].
Postoperative Intravesical Chemotherapy involves the administration of chemotherapeutic agents into the bladder within 6 hours after the end of TURB. Although this strategy has a clear impact on the recurrence rate, it is less effective than BCG.
The most commonly used agents for postoperative chemotherapy are Mitomycin C, anthracyclines, Thiotepa, Gemcitabine, and Apaziquone (a precursor to Mitomycin C) [18].
The purpose of this procedure is to remove any visible bladder tumor and sample any suspicious areas for biopsy. Typically, a deep resection is performed to remove a part of the detrusor muscle as well [15].
Radical cystectomy (RC) is a highly recommended treatment option for patients in the following scenarios:
1. When high-grade non-muscle invasive bladder carcinoma has extensively invaded the lamina propria.
2. When lymphatic metastases are present.
3. When the cancer involves the distal part of the ureters or prostatic urethra.
4. When cancer are resistant to initial treatment [19].

RC is considered the most effective treatment for muscle-invasive or metastatic bladder cancer. In men, it typically involves the complete removal of the bladder, seminal vesicles, prostate, and potentially bilateral inguinal lymph nodes. In women, it involves the complete removal of the uterus and adnexa, and all or part of the vagina [20] [21].

ANESTHESIOLOGICAL TECHNIQUES

Locoregional anesthesia is a safe and effective technique that reduces the risk of postoperative respiratory and cardiovascular complications [22]. It facilitates the restoration of normal bowel function [23], reduces intraoperative blood loss, and is associated with good postoperative pain control with minimal or no opioid use [24]. SpEA, a combination of two techniques, offers several benefits. For a good analgesic endpoint, a peridural catheter is placed at the thoracic level (T11-T12), and low-dose subarachnoid anesthesia is performed concomitantly. The latter produces motor and sensory blockade, which enables the surgery to start in a shorter time, and the low dose allows for fewer hemodynamic implications.

Spinal anesthesia produces sensory and motor blockade, and the total duration of surgical anesthesia depends on the dose, the intrinsic properties of the anesthetic used, and the use of adjuvant drugs. Additionally, the epidural catheter enables the administration of additional doses of local anesthetic intraoperatively (if needed) and postoperative pain management.

During spinal anesthesia, neuroaxial blockade is produced by interrupting nerve impulse transmission with the administration of a local anesthetic.

When a drug is injected directly into the subarachnoid space, it passes through the pia mater and enters the Virchow-Robin orifices to reach the deeper dorsal root nerve ganglion. These nerve endings are highly accessible and can be easily anesthetized even with a low dose of local anesthetic, in contrast to extradural nerves. The speed of spinal block depends on the size, surface area, and degree of myelination of the fibers exposed to the anesthetic. However, the desired effect may regress or cease when the concentration of the drug within the cerebrospinal fluid decreases, that is, when the blood vessels in the pia mater absorb the substances into the systemic circulation, to be metabolized and excreted. The rate of elimination depends on the distribution of the local anesthetic. If the surface area of diffusion is greater, the exposure of the drug to the vessels increases, and thus the time of drug action will be shorter.

Bupivacaine is one of the most widely used local anesthetics for spinal anesthesia. It has high protein binding and slow onset due to its relatively high pKa. Standard doses for clinical practice make it appropriate for surgical procedures with timings between 150 and 180 minutes.

The use of intravenous dexmedetomidine in combination with local anesthesia can result in a reduction of the required dosage of both analgesics and sedatives during surgery and in the initial postoperative period. This technique has been found to be particularly effective in sedating patients, reducing discomfort associated with prolonged periods on the operating table, or cognitive deficits that are often present in patients over 80 years old, such as multi-infarct ischemia, which may make it difficult for them to tolerate medium to long duration surgeries. For instance, for cystectomy, which can take an average of 90 to 200 minutes to perform, this technique can be helpful. However, this technique has some limitations, including absolute rejection by the patient, inability to perform the technique in patients with severe spinal pathologies, and inexperience of the performer. A study by Karl indicates that the exclusive use of locoregional techniques is recommended for performing radical cystectomy in patients with high comorbidities, for whom performing the procedure under general anesthesia would be too risky. [25]

It is crucial to focus on the fast-track regimen that is recommended for patients of this type. A study has demonstrated that a combined spinoepidural technique (SpEA), which involves keeping the patient awake and breathing spontaneously throughout the procedure, can greatly reduce the risk of perioperative complications in patients undergoing RC with extensive iliac lymph node involvement and urinary diversion. This technique is beneficial as it does not interfere with the cardiopulmonary system and, when combined with a short surgical time, it results in low blood loss and rapid channeling, feeding, and mobilization of the patient.

To execute a successful technique, it is important to evaluate individual patient characteristics such as age, sex, body mass index, tumor stage, comorbidities, cardiopulmonary risk assessment, as well as intraoperative and postoperative parameters. It is also essential to consider the type of surgical technique, operative time, blood loss, and adequate postoperative pain management.

Patients who are taking oral anticoagulants should be treated with low molecular weight heparin, with a dosage reduction immediately before and after surgery (a waiting period of 10-12 hours in pre and postoperative).

Throughout the anesthesiological and surgical procedure, blood pressure, heart rate, and SpO2 should be continuously monitored.

During surgery, the patient's body temperature is regulated through the use of heated blankets instead of hot fluids to prevent potential vasodilation, especially in the early stages. Prior to performing epidural anesthesia (SpEA), no intravenous premedication is administered. However, 2% lidocaine is infiltrated into the injection site at a rate of 1-2 ml per space.

The SpEA procedure involves placing the thoracic epidural catheter at either T10/11 or T11/12, followed by spinal anesthesia at the L2/L3 or L3/L5 level. This can be done with the patient sitting or lying down in the lateral position, and the procedure is performed in two stages. First, the epidural space is identified by puncturing it with a Tuohy G17 epidural needle between two spinous processes included in the T10-T11 or T11-T12 space after local anesthesia. The needle is inserted through the skin, intervertebral ligaments, and yellow ligament.

The "loss of resistance" technique is used to identify the epidural space. This can be done with a liquid chuck, in which the syringe present in the kit is filled with saline solution, or with an air chuck, which only uses air. We prefer the liquid chuck technique as the air chuck technique has a minimal risk of pneumoencephalus.

When administering an epidural, Tuohy's needle is used to slowly advance the syringe connected with Thouy's needle through the spine's ligaments, usually 4-5 cm. It may encounter some resistance, but once the loss of resistance indicates negative pressure, the epidural space has been located. Then, a thin plastic catheter is inserted through Tuohy's needle and left in the epidural space. This catheter can be anchored in the subcutis for better protection against infection and stability in the postoperative period. Alternatively, it can be fixed to the skin with a special dressing found in some kits. After surgery, the epidural catheter is removed approximately 24 hours later.

Following the placement of the catheter, a test dose with lidocaine 2% 3ml is administered to exclude accidental placement in the subarachnoid space. The correct placement of the peridural catheter is crucial for both the surgical procedure and effective postoperative pain management. This is because it allows for the tailoring of anesthesia to the duration of surgery. Furthermore, a variable-flow elastomer with continuously infused local anesthetic is attached to it for postoperative pain management.

Spinal anesthesia is performed while the patient is seated. A whitacre needle with G25 introducer is inserted in the lumbar vertebral area between L2/L3 or L3/L4. The needle is advanced through the layers of the spinous processes until it reaches the subarachnoid space. The presence of Cerebrospinal fluid through the needle indicates that the procedure has been done correctly. At this point, the patient is injected with local anesthetic, the effect is almost immediate, with a warm, tingling sensation in the feet and legs. Anesthesia and analgesia occur within minutes, accompanied by sensory and motor blockade. The duration of effect is about 120-180 min. The effectiveness of SpEA depends on the dose of drug administered, and nerve block occurs in this order: sensory fibers, cold sensation, sympathetic fibers, vasomotor, and motor.

All patients breathe spontaneously during the entire surgical procedure. Intravenous sedation is also administered to all patients. There are studies in which propofol is given as a continuous infusion at a dosage of 0.5-1 mg/kg body weight/hr.

In our study, we chose to use dexdor as the drug for intraoperative sedation.

For postoperative pain management epidural catheter is important to administer local anestethic through the use of variable-dose elastomeric pumps. This ensured excellent postoperative pain management, with VAS 2-3 in treated patients.

The epidural catheter is usually removed 24 hours after the surgery and 12 hours after the last heparin dose. Thankfully, we did not come across any complications like epidural hematomas.

This anesthetic approach enabled us to initiate postoperative mobilization and early enteral feeding in adherence with the fast-track concept.

During hospital stay, we collected feedback from patients on the pre-, intra-, and post-operative procedures. All patients reported being highly satisfied with the procedures performed and the pain management during the perioperative period.

All procedures were carried out without any anesthetic or surgical complications, as planned preoperatively. The vital parameters of all patients remained stable both during and after the operation. It is worth highlighting that from an anesthetic perspective, the use of a SpEA is more effective than general anesthesia. According to a meta-analysis [26], neuraxial blockade significantly reduces mortality rates due to a reduction in the incidence of deep vein thrombosis, pulmonary embolism, myocardial infarction, transfusions, pneumonia, infections, respiratory depression and liver failure [27] [28]

[29]. Additionally, the cardiorespiratory implications present during general anesthesia are reduced, which is highly beneficial for patients with high cardiopulmonary risk.
For surgical procedures involving sensory blockade up to T10 (medium-high anesthesia) in the lower abdomen and lower limbs, spinal anesthesia is today considered a safe and established method, primarily applied to elderly and/or high-risk patients [24] [30]. Techniques like SpEA have an additional beneficial effect compared to local anesthetic applied only epidurally [31].
The combination of single spinal anesthesia (also known as "single shot") and continuous thoracic epidural anesthesia is a great option for surgeries. Injecting local anesthetic into the subarachnoid space provides quick and reliable pain relief and good muscle relaxation during the surgery. Unlike continuous administration, injecting the anesthetic only once via epidural catheter prevents long-lasting motor block which can delay early mobilization. [24]
Epidural anesthesia also helps manage postoperative pain through the catheter. Studies have shown that epidural anesthesia is better than intravenous and/or intramuscular administration of opioids [31] [32] for intra-abdominal procedures, with a lower risk of paralytic ileus at 72 hours.
Spinal-Epidural anesthesia reduces postoperative morbidity and mortality, and it combines the advantages of spinal anesthesia with a rapid anesthetic effect and effective motor block for surgery, as well as control over post-operative analgesia through the epidural catheter. [28] [33] [34]
However, undesirable side effects of SpEA may include hypotension, cerebral ischemia, bradycardia, cardiac arrhythmia, cardiac arrest (in rare cases), respiratory failure due to high spinal anesthesia, paraplegia following an epidural hematoma or arachnoid abscesses, nausea and vomiting, motor block, pruritus, and post-dural puncture headache (PDPH). [35] [36]
During our surgeries, we observed mild hypotension as the only undesirable side effect. In some cases, longer surgical times, hypothermia, and inadequate positioning on the operating bed can also cause discomfort for the patient, but SpEA can be tolerated with a progressive increase in sedation.
Mild to moderate sedation in combination with SpEA is an effective technique for radical cystectomy, as it maintains spontaneous breathing and reduces interference with the cardiopulmonary system.

SEDATION

In order to improve the comfort of patients who are undergoing major abdominal surgery using locoregional techniques, many studies have been conducted using intravenous drugs for intraoperative sedation. It is common practice to administer drugs like propofol or remifentanil, but we chose not to use these routinely as they are opioids, and we wanted to minimize their use in accordance with the ERAS protocol.
Instead, we opted for dexmedetomidine, a drug that is mainly used in Europe for sedation in intensive care units, but has also been reported to be effective during general anesthesia. A study from 2017 by Arthur Davy , Julien Fessler, [37] reported the use of dexmedetomidine in adults undergoing general anesthesia, and described several potential uses of the drug, such as awake fiberoptic intubation, as an adjuvant effect on sparing hypnotic and opioid drugs, for the prevention of post-operative pain, nausea, vomiting and chills, in improving sleep and post-operative recovery, due to opioid-free anesthesia. The drug has also been shown to have protective effects against cardiac complications and an anti-inflammatory effect. It is important to note that studies relating to cardiac surgery and those reporting the use of dexmedetomidine as an adjunct to regional anesthesia were excluded from this study.
Dexmedetomidine is a medication that acts as an alpha-2 adrenergic agonist, providing both sedative and analgesic effects. Its mechanism of action affects the alpha-2 receptors present in the dorsal horn of the spinal cord, both pre- and post-synaptically. It reduces the release of neurotransmitters, leading to a reduction in the transmission of impulses. This, in turn, leads to a hypnotic, sympatholytic, and analgesic effect.
When administered through intravenous infusion, dexmedetomidine has the ability to cause light sedation, with patients remaining responsive to verbal or tactile stimuli. Its effectiveness has been tested for spinal anesthesia with local anesthetics, through bolus administration followed by maintenance infusion at variable doses per kilogram. This therapy has been found to be beneficial for several periumbilical surgeries, such as varicocelectomy, hernioplasty, orchiectomy, and lower extremity surgeries. The use of dexmedetomidine has been proven to reduce the risk of nausea, vomiting, headache, and chills. It provides longer-lasting nerve block and postoperative analgesia, thereby

reducing the consumption of sedative drugs and opioids from the beginning of surgery until the first 24 hours after the surgery.

Finally, the administration of this drug has been reported to cause hypotension and bradycardia in some populations. However, these side effects are rare and can be easily reversed with the use of commonly used hemodynamic drugs such as atropine and ephedrine. In daily clinical practice, different responses are often observed following the administration of the drug, which can be attributed to individual differences in the pharmacokinetics of the drug. These differences can be linked to race, ethnicity, and social habits, which can lead to enzymatic variations or genetic polymorphisms. Nevertheless, the combination of spinal anesthesia and intravenous dexmedetomidine is a safe option for patients with stable hemodynamics undergoing elective surgery.

There is an ongoing randomized double-blind study [38] that aims to compare the total duration of neuraxial block with spinal hyperbaric bupivacaine and the use of intravenous dexmedetomidine, with the administration of hyperbaric bupivacaine alone. The study includes 60 patients aged between 18 and 65 years, classified by the American Society of Anesthesiologists (ASA) I and II, who are undergoing an elective orthopedic procedure of the lower limbs with spinal anesthesia plus an epidural catheter. Fifty percent of patients (group A) will receive hyperbaric bupivacaine and dexmedetomidine IV at 0.5 mcg/kg (actual weight), and the other 50% (group B) will receive spinal hyperbaric bupivacaine and 0.9% saline IV in an equivalent volume. The objective of the study is to understand whether dexmedetomidine can be used routinely as an adjuvant to prolong the duration and improve the anesthetic and analgesic characteristics of a neuraxial block with intrathecal bupivacaine in orthopedic surgery of the lower limbs. In our study, we also aim to evaluate the intravenous use of dexmedetomidine as an adjuvant to anesthesia, in accordance with the ERAS protocol. We initially administered it at a dosage of 0.7 mcg/kg/h, which we later reduced to 0.4/mcg/kg/h based on BIS monitoring. This was done to limit the side effects of the drug. Some patients experienced hypotension (a side effect of sympathetic blockade) about 15 minutes after subarachnoid puncture. To treat this, we promptly administered a minimal dose of ephedrine or bradycardia with HR < 40 bpm after infusion of dexdor at 0.7/mcg/kg/h. For this reason, we reduced the dosage to 0.4 mcg/kg/h.

In very elderly patients, marked bradycardia responsive to atropine administration and discontinuation of the drug itself can be observed. However, dexdor is a very manageable drug that does not cause respiratory depression. It allows for a sedated

patient throughout the procedure, easily awakened to verbal stimulus and with a complete orientation in time and space.

PROTOCOLLO ERAS

The ERAS protocol, [39] which stands for Enhanced Recovery After Surgery, is a method aimed at reducing surgical stress and maintaining the patient's body homeostasis to enable quick post-operative recovery. The protocol includes a complete path for the patient, starting from the moment they are hospitalized and involves the surgeon's consultation, accurate anamnesis and examination, staging tests, basic blood tests, evaluation of the social aspect, the fragility of the patient, and their nutritional state.

The ERAS protocol is based on the following foundations:

• Preoperative counseling

• Prehabilitation

• Minimally invasive surgical techniques

• Optimal pain control with a multimodal approach

• Early post-operative rehabilitation

The main objectives of the ERAS protocol are:

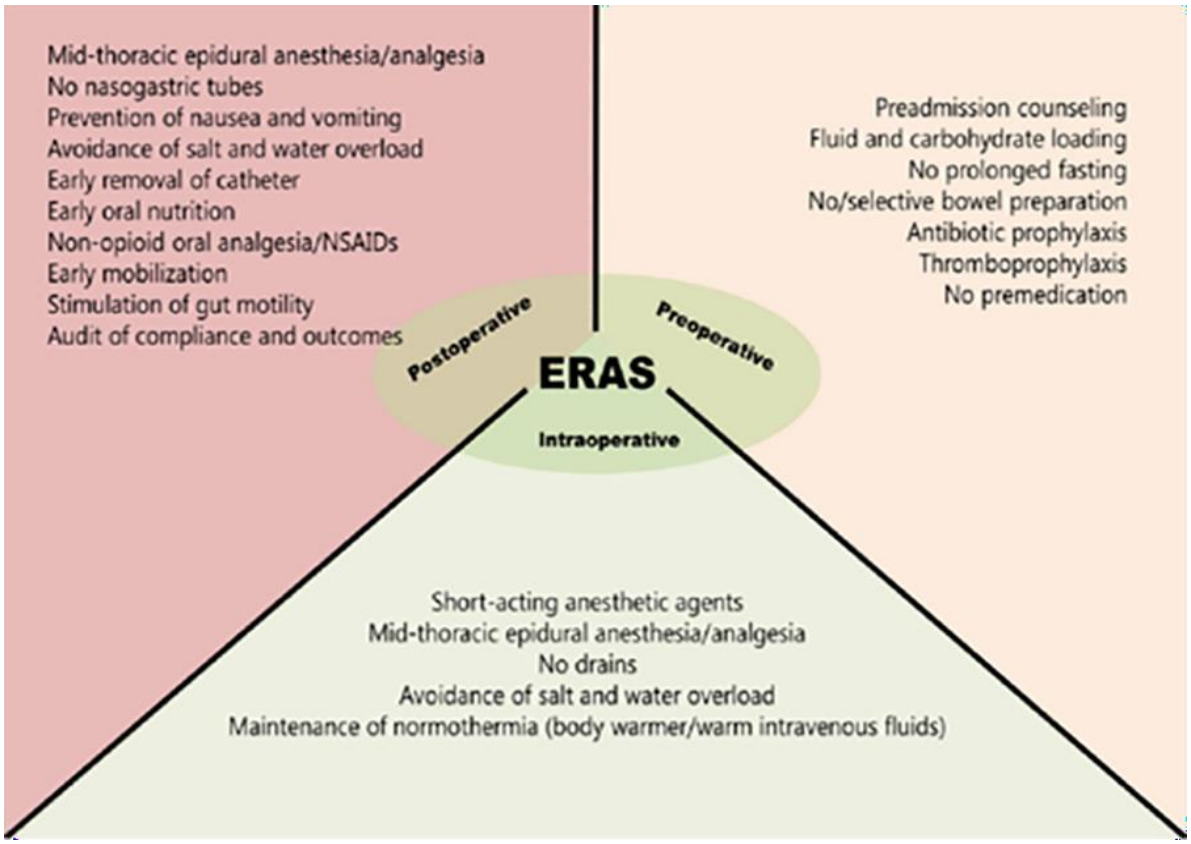
• To optimize perioperative management using evidence-based procedures

• To promote a better post-operative recovery of the patient's autonomy

• To reduce hospitalization times

• To increase patient satisfaction with the care provided

• To decrease the incidence of complications, hospital readmissions, and costs.



The pre-operative evaluation and information, including the anesthetic visit, occurs about two weeks prior to surgery, [40]. During this visit, the focus is on stabilizing any clinical conditions such as cardiological diseases, anemia, COPD, diabetes, and states of nutritional deficiencies. The patient is encouraged, with adequate support, to abstain from smoking and alcohol.

For patients who have a history of severe respiratory disease (COPD, asthma, sleep apnea syndrome), an instrumental clinical evaluation of respiratory function will be conducted to identify subjects who could benefit from pre- and/or post-operative physiotherapy treatment.

It is important to have a pre-operative counseling session where the patient meets with the multidisciplinary team consisting of the surgeon and anesthetist. This session provides all the information needed on the procedures of relative competence (anaesthesiological and surgical). Family members are also involved to evaluate the best strategy to implement. It is advisable to have verbal information supplemented with prepared material.

This process is useful for identifying any critical issues in perioperative management and evaluating preoperative anesthetic risk based on the American Society of Anesthesiologists classification (ASA score).

Class	Description	Example
I	**The patient was previously healthy and fit**	Healthy, non-smoking, no or minimal alcohol use
II	**The patient has mild systemic controlled disease**	Mild diseases only without substantive functional limitations. Examples include (but not limited to): current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
III	**The patient has severe but not incapacitating systemic disease**	Substantive functional limitations; one or more moderate to severe diseases. Examples include (but not limited to): poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3 months) of MI, CVA, TIA, or CAD/stents
IV	**The patient has incapacitating systemic disease**	Examples include (but not limited to): recent (< 3 months) MI, CVA, TIA, or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, sepsis, DIC, ARD or ESRD not undergoing regularly scheduled dialysis
V	**The patient is moribund not expected to survive 24 hours**	Examples include (but not limited to): ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction

On the day before surgery, there are no food restrictions, although clear liquids can be consumed up to 2 hours before the surgery. Patients should take antithrombotic and antibiotic prophylaxis, and it is important to prevent anemia.

During the operation, pre-anesthesia is generally not administered. In laparotomy surgery, an epidural catheter is positioned and subarachnoid anesthesia is executed. Dexmedetomidine is used for intraoperative sedation.

Intraoperative hydration is limited, with crystalloid solutions given at a dosage of 4 ml/kg/h. Maintaining a diuresis of at least 0.5 ml/kg/h is important, as well as preventing hypothermia. Prophylaxis of nausea and vomiting is also necessary.

If the epidural catheter cannot be positioned, opioid-sparing analgesic strategies are preferred. The bladder catheter is placed after the SpEA has been performed. Minimally invasive laparoscopic techniques are preferred, where possible, or minilaparotomies. [41]
Drain placement may be necessary in cases of increased risk of bleeding or dehiscence of intestinal anastomosis.

After a surgical procedure [42],

- it is important to: monitor the patient's breathing and oxygen levels for at least an hour.
- Low flow oxygen therapy can be provided until the following morning.
- Pain assessment,
- temperature control,
- early nutrition and infusion therapy,
- fluid infusion on the first post-operative day of approximately 1-2 ml/kg/hour,
- removal of intravenous infusions within the first postoperative day are all part of the postoperative management.

If the patient cannot eat early on, infusion therapy must be maintained and adjusted according to oral fluid intake, and can be reintroduced normally two hours after the surgical procedure or on the evening of the operation, depending on the end time of the surgical procedure. On the first day, ideally, the patient can drink up to 2 liters of liquids while increasing their diet. Early mobilization occurs 24 hours after surgery or after removal of the epidural catheter and early removal of the bladder catheter. Analgesia or pain relief must be integrated with paracetamol 1 g iv (maximum 3 g/day), and after removal of the epidural catheter, with NSAIDs as needed. If the epidural catheter has not been positioned, NSAIDs + paracetamol are prescribed from the first hours post-operatively. If the use of major opioids is not

recommended, they should be associated with adequate antiemetic therapy to ensure fluid intake and oral nutrition.

Multimodal pharmacological therapy, such as cortisone and Ondansetron, is necessary for optimal control of symptoms like nausea and vomiting. The eligibility assessment for post-operative recovery depends on adequate nutrition, pain control, recovery of intestinal function, and self-sufficiency.

ERAS protocols can help reduce physical stress reactions caused by pathological states, with special attention to elderly patients with comorbidities. [43]

Adopting the ERAS protocol has been shown to reduce postoperative complications by 50%, decrease length of stay by 30%, and lower hospital readmission rates, leading to a reduction in healthcare costs. [44]

BIOMARKERS

Aside from clinical aspects, the study aimed to identify biomarkers of inflammation related to oncological pathology, such as Neutophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR), to determine if there was any variation in inflammatory indices between the two anesthetic techniques used.

Inflammation is a critical factor in the outcome of oncological pathology, and various inflammatory indices have been examined over the last decade to improve patient stratification for treatment and positively impact survival. The neutrophil/lymphocyte ratio (NLR) is a frequently used marker for assessing the systemic inflammatory response. It is derived from the absolute neutrophil and absolute lymphocyte counts of a complete blood count. This provides insight into the balance between neutrophil-associated pro-tumor inflammation and lymphocyte-dependent immune function.

NLR is a reliable and economical marker of cancer-related inflammation and a valid indicator of prognosis of solid tumors. It is used for cancer stratification, is correlated with tumor size, stage, metastatic potential, and lymphatic invasion. It also has a role as an independent prognostic factor for overall, cancer-free, and cancer-specific survival. [45]

The normal range for NLR values is between 1-2. In adults, values higher than 3.0 and lower than 0.7 are considered pathological. A range between 2.3-3.0 is an early indicator of a pathological state such as cancer, atherosclerosis, infection, inflammation, psychiatric disorders, and stress. Most meta-analyses have established the cut-off value of NLR as greater than 3.0 for various solid tumors, indicating a pathological state. NLR values of 6-9 suggest mild stress, while values above 9 are present in critically ill patients.

Another biomarker that combines the pre-inflammatory state of cancer with the residual endogenous resistance of cancer itself is the platelet-to-lymphocyte ratio (PLR). Its normal value ranges between 90 and 210. Several authors have evaluated the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) in bladder tumors.

In the study by Claps et al [46], the preoperative immuno-inflammatory response described by NLR, PLR, LMR, SII, and CRP showed low reliability in predicting the

perioperative course after RC. Meanwhile, Ziani's study defines how preoperative NLR value could predict the recurrence, progression, and failure of BCG immunotherapy in NMIBC patients [47].

In Ahmad Zulfan Hendri's study, the prognostic capacity of baseline NLR associated with PD-L2 expression in bladder cancer was evaluated. Patients were classified based on their levels of PD-L2 and NLR, and the prognostic outcome of each group was associated with disease-free survival and overall survival. However, no significant correlation was found between PD-L2 expression and NLR. PD-L2 and NLR status failed to provide significant prognostic impact. However, when PD-L2 status and NLR status were correlated, NLR-low and PD-L2-low were considered significant factors in predicting favorable disease-free survival [48]

STUDY

The objectives of this exploratory, [49] controlled study were (1) to further evaluate the feasibility of combined spinal and epidural anaesthesia (SpEA) and (2) to compare perioperative outcomes between SpEA and standard GA in patients undergoing ORC(3) to evaluate the impact of different type of anesthesia on laboratory tests

Patients

A prospectively maintained database for RC patients collecting clinical, oncological and functional data has been active at the University of Messina Urology Section since 1 May 2017. For the purpose of the present comparative, non-randomised study, 60 consecutive patients with bladder cancer scheduled for ORC from sMay 2020 were selected, and one every three patients was assigned to the study group. The study group, thus, included 15 patients undergoing surgery with SpEA, and the control group was composed by 45 patients being operated on under GA. Exclusion criteria were contraindications for SpEA, such as skin infection at the site of spinal and/or epidural puncture, severe coagulopathies and spinal disorders. After discussion with an anaesthesiologist and a treating surgeon, patients agreed to participate in the study by signing an informed consent where they accepted the possibility to receive SpEA instead of GA and authorised data collection for scientific purposes. All patients had computed tomography of thorax, abdomen and pelvis for staging purpose.

Anaesthesia techniques

ORC including extended pelvic lymph node dissection and urinary diversion (orthotopic ileal neobladder, retrosigmoid ileal conduit or cutaneous ureterostomy) was performed by a single expert surgeon via an infraumbilical incision according to previously described surgical techniques. [50] [51]

Both SpEA and GA were performed by two dedicated anaesthesiologists with extensive experience in both loco-regional anaesthesia and GA techniques. Patients in the study

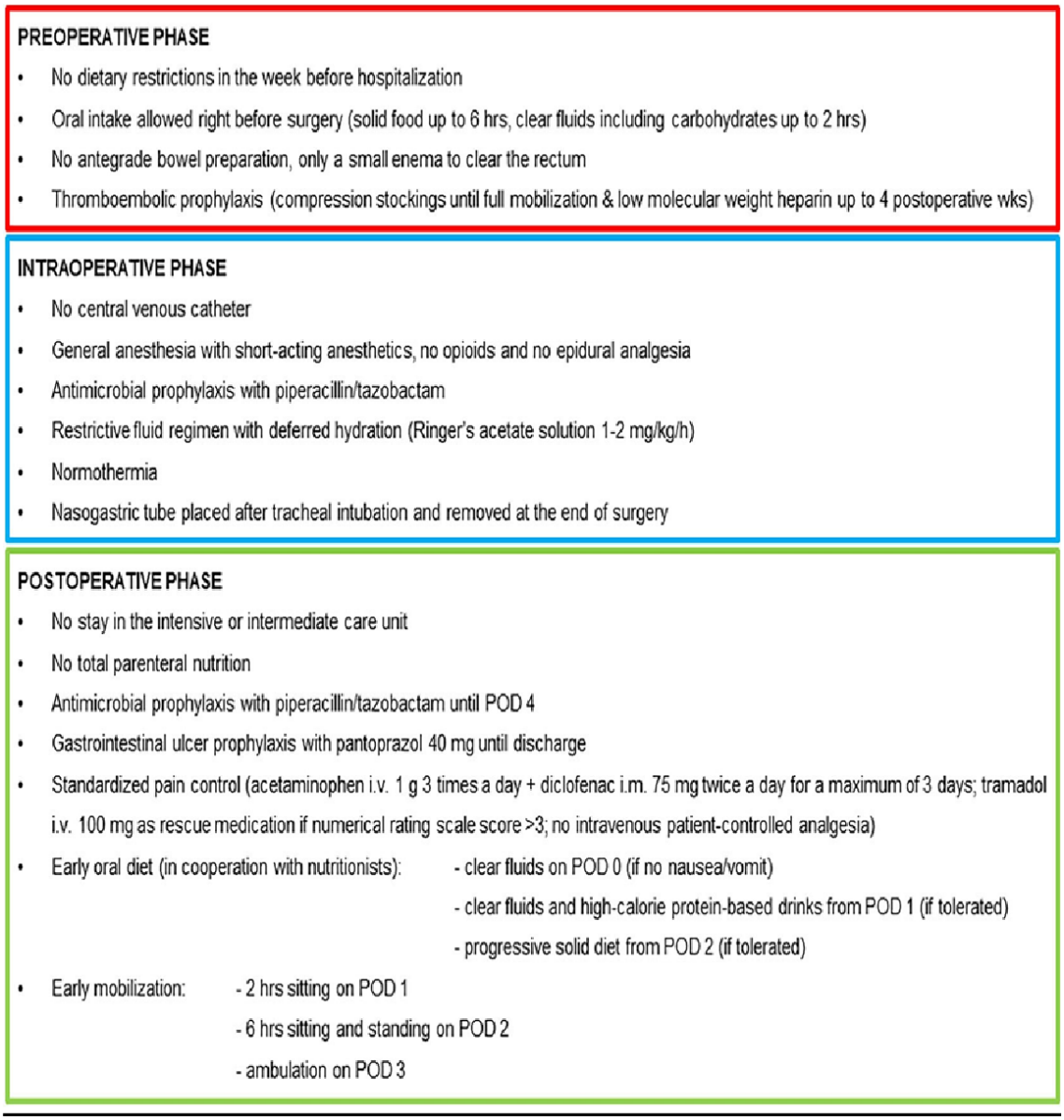
group received pure SpEA. With patients in a sitting position, a deep thoracic epidural catheter was placed at Th10– 11 or Th11–12 level through a 17-G Tuohy needle. Spinal anaesthesia was administered by puncturing the space between L2–3 and L3–4 with a 25-G Whitacre needle with introducer and infusing 3 ml levobupivacaine 0.5% (15 mg) and 10 μg fentanyl. During surgery, 5 ml ropivacaine 7.5% (37.5 mg) with 4 ml saline 0.9% and 50 μg fentanyl every 2–3 h were administered. Although patients breathed spontaneously during the entire surgical procedure, they received an escalating i.v. sedation with dexmedetomidine under continuous measurement of bispectral index to monitor its depth, with a target value of 65–55. Dexmedetomidine was infused at 0.7 μg/kg/h velocity with on-demand adjustments of +/ 0.1–0.2 μg/kg/h. This enabled patients to sleep, to be responsive to verbal stimuli and to maintain a slow and shallow breathing. Patients included in the control group received a standard balanced GA. Induction was performed with i.v. propofol (1.5–2.5 mg/kg) combined with i.v. fentanyl (2–3 μg/kg) and i.v. rocuronium bromide (0.6–1.0 mg/kg). No benzodiazepines were used. Maintenance was performed with i.v. sevoflurane (1–2%), and i.v. remifentanil in continuous infusion (0.05–0.20 μg/kg/min). A valid neuromuscular block was achieved through repeated i.v. rocuronium bromide boluses (0.1–0.2 mg/kg).

Postoperative management

Postoperative pain control was standardised. In the first 24 h, in the study group, 5–6 ml/h ropivacaine 2 mg/ml was infused through theepidural catheter, which was then removed. In the control group, continuous i.v. infusion of chlorinated tramadol 200 mg and ketorolac 60 mg 2 ml/h was administered. The i.m. morphine 1 mg/10 kg was given as a rescue medication if VAS score was >3. After 24 h, patients in both groups received i.v. acetaminophen 1 g three times a day and i.m. diclofenac 75 mg twice a day for further 3 days. The i.v. chlorinated tramadol 100 mg was given as a rescue medication if VAS score was >3. No intravenous patient-controlled analgesia was used. An Enhanced Recovery after Surgery (ERAS) pathway was followed as previously described.14 Briefly, in addition to opioid-sparing anaesthesia and analgesia, the protocol included no preoperative dietary restrictions, no bowel preparation, no nasogastric tube, no postoperative stay in the intensive or intermediate care unit, no total

parenteral nutrition, early nutritionist-guided oral diet and early mobilization. Details are reported in (Figure 1).

FIGURE 1 Details of the enhanced recovery pathway after open radical cystectomy adopted at our institution for patients receiving generalanaesthesia



Data collection and study outcomes

The following variables were prospectively collected: age on surgery, gender, body mass index, Charlson comorbidity index, haemoglobin and creatinine levels, clinical tumour and node stage according to the 2017 TNM staging system, American Society of Anesthesiologists (ASA) score, intraoperative colloid and crystalloid infusion, EBL, intraoperative red blood cell transfusion rate, anaesthesia time (including induction, surgery and recovery), surgery time (divided by RC and urinary diversion) and intraoperative complications.

We recorded the following laboratory parameters: eGFR, neutrophilic/lymphocytic ratio and platelet/lymphocytic ratio. Each parameter was tested before surgery (preoperative evaluation), 48 hours after surgery (post-operative evaluation) and at patient's discharge (final evaluation). Moreover, we calculated the Δ between preoperative values and post-operative values as well as between preoperative and final values.

All surgical specimens were processed according to the standard protocol and reviewed by a dedicated uropathologist. The following parameters were assigned: cell type, tumour and nodal stage according to the 2017 TNM staging system, urethral and soft tissue surgical margin status and perineural and lymphovascular invasion. Pain level was assessed 24 h postoperatively by a rotating anaesthesiology resident not involved in the study team using a 10-point visual analogue scale (VAS) graduating 0 = no pain and 10 = worst pain. Number of patients requiring rescue medication and time to first rescue medication within the first postoperative 24 h and during the subsequent 3 days [postoperative day (POD) 1 to 4] were also recorded. Other postoperative parameters were oxygen saturation percentage (SpO2) in room air measured by pulse oximetry in holding area before readmission to the ward, ERAS compliance, nasogastric tube placement due to nausea/vomiting or ileus, time to return to oral diet, time to bowel function recovery (measured as resumption of bowel sounds, passage of flatus and passage of stool), time to ambulation and LOS.

Postoperative complications observed within 90 days from surgery were recorded and graded according to the Clavien–Dindo classification [52]. Grade 1 or 2 complications were considered as minor, and Grade 3 to 5 complications were classified as major. Specific SpEA-related complications were also recorded.

Statistical analyses

The premises for the above study design were the scarcity of literature data on the role of loco-regional anaesthesia in patients undergoing RC with only very few feasibility studies, the lack of comparative controlled studies and the still exploratory nature of our analysis. The 1:3 assignment ratio was conceived to resemble a semi-randomised study, while limiting the number of patients in the study group receiving a still experimental anaesthesia technique with potential safety issues. For all these reasons, an RCT with a formal sample size calculation was deemed not justified at the current stage of the research. Furthermore, no formal distinction between primary and secondary study outcomes was made, under the assumption that all above reported variables might be of potential interest to correctly appraise the tested anaesthesia technique. Parametric continuous variables were reported as means ± standard deviation, whereas median and interquartile range (IQR) were used for non-parametric continuous variables. Student's t-test, Mann–Whitney U test and Pearson's chi-square test were used to compare continuous parametric, non-parametric and categorical variables, respectively, as appropriate. All the laboratory parameters were reported as median values and interquartile range (IQR). The Wilcoxon and Friedman tests were used to compare 2 or more non-parametric, correlated variables, respectively. All clinical records were inserted in a dedicated database, and data were analysed using SPSS v. 21.0 software (IBM Corp., Armonk, NY). All reported p values were two-sided, and statistical significance was set at $p < 0.05$. 3

Results

The study period terminated on 31 December 2021. No patients were excluded from the study as per exclusion criteria. No patients assigned to the study group refused the proposed anaesthesia technique after signing the informed consent. Moreover, there was no technical failure in spinal puncture or epidural catheter placement in the study group. Therefore, no patients assigned to the study group crossed over to the control one. The two groups were comparable for all demographic, clinical and pathological characteristics. Moreover, no differences were detected in terms of urinary diversion receive. (Table 1)

TABLE 1 Demographic, clinical and pathological characteristics of the 60 patients included in the comparative analysis stratified by type ofanaesthesia technique during open radical cystectomy

Variables	Study group (n = 15)	Control group (n = 45)	p value
Gender (n, %)			0.84
• Male	12 (80%)	37 (82.2%)	
• Female	3 (20%)	8 (17.8%)	
Median (IQR) age (years)	72 (68-79)	73 (63.5-79.5)	0.70
Median (IQR) body mass index (kg/m^2)	23 (21.4-25)	26.3 (22.5-28)	0.11
Charlson comorbidity index (n, %)			0.29
• ≤1	10 (66.7%)	23 (51.1%)	
• >1	5 (33.3%)	22 (48.9%)	
Clinical tumour stage (n, %)			0.66
• cTa/cT1/Cis	2 (13.3%)	5 (11.1%)	
• cT2	11 (73.3%)	29 (64.4%)	
• cT3-4	2 (13.4%)	11 (24.4%)	
Clinical node stage (n, %)			0.78
• cN0	14 (93.3%)	41 (91.1%)	
• cN1	1 (6.7%)	4 (8.9%)	
Median (IQR) haemoglobin level (g/dl)	12 (10-13.3)	11.7 (9.5-13.6)	0.95
Median (IQR) serum creatinine level (mg/dl)	1 (0.8-1.7)	1.2 (0.9-1.5)	0.26
Median (IQR) estimated glomerular filtration rate (ml/min)	65 (37-91)	53 (33.4-75.6)	0.37
ASA score (n, %)			0.40
• 2	3 (20%)	14 (31.1%)	
• 3	12 (80%)	31 (68.9%)	
Urinary diversion (n, %)			0.92
• Ileal neobladder	3 (20%)	7 (15.6%)	
• Ileal conduit	8 (53.3%)	25 (55.6%)	
1. Cutaneous ureterostomy	4 (26.7%)	13 (28.9%)	
Histologic subtype (n, %)			0.18
• Urothelial	10 (66.7%)	34 (75.6%)	
• Squamous	3 (20%)	1 (2.2%)	
• Micropapillary	1 (6.7%)	1 (2.2%)	
• Microcystic	0	1 (2.2%)	
• Nested	1 (6.7%)	6 (13.3%)	
• Plasmacytoid	0	2 (4.4%)	
Perineural invasion (n, %)			0.07
• Absent	14 (93.3%)	32 (71.1%)	
• Present	1 (6.7%)	13 (28.9%)	
Lymphovascular invasion (n, %)			0.13
• Absent	10 (66.7%)	20 (44.4%)	
• Present	5 (93.3%)	25 (55.6%)	
Pathological tumour stage (n, %)			0.15
• pTis	1 (6.7%)	4 (8.9%)	
• pT1	2 (13.3%)	9 (20%)	
• pT2	5 (33.3%)	11 (24.4%)	
• pT3	7 (46.7%)	10 (22.2%)	
• pT4	0	11 (24.4%)	
Pathological node stage (n, %)			0.21
• pN0	12 (80%)	35 (77.8%)	
1. pN1	3 (20%)	10 (22.2%)	

Abbreviations: ASA, American Society of Anesthesiologists; Cis, carcinoma in situ, IQR, interquartile range.

No patients required conversion from SpEA to GA for surgical or anaesthesiology issues. In the study group, all patients breathed spontaneously, were responsive to verbal stimuli and had bispectral index values ranging between 50 and 65, which correspond to adequate anaesthesia during surgery. Both abdominal wall and bowel were adequately relaxed during the entire procedure. Intraoperative vital signs of patients in both groups were stable. No patients in the study group showed hypotension as a potential side effect of the sympathetic blockade. Hypotension was detected and promptly managed only in one patient in the control group. No intraoperative complications were recorded, and no significant differences were observed between the two groups with regard to other intraoperative parameters, except for a shorter anaesthesia time in the study group (Table 2).

TABLE 2 Intraoperative variables for the 60 patients included in the comparative analysis stratified by type of anaesthesia technique duringopen radical cystectomy

Variables	Study group(n = 15)	Control group(n = 45)	p value
Median (IQR) crystalloid infusion (ml)	2500 (1500-2500)	2200 (2000-2500)	0.30
Colloid infusion (polygelin) (n, %)	0 (0%)	3 (6.7%)	0.91
Median (IQR) estimated blood loss (ml)	400 (300-500)	400 (300-400)	0.98
Red blood cell transfusion (n, %)	3 (20%)	6 (13.3%)	0.53
Median (IQR) anaesthesia time (min)	250 (200-280)	290 (235-310)	0.01
Median (IQR) radical cystectomy time (min)	150 (120-180)	150 (120-170)	0.95
Median (IQR) urinary diversion time (min)	80 (20-100)	80 (27-80)	0.63

Abbreviation: IQR, interquartile range.

Postoperative SpO2 was comparable in the two groups ($p = 0.12$). Pain VAS score 24 h after surgery was significantly lower in the study versus control group ($p < 0.001$) (Table 3).

TABL E 3 Postoperative variables for the 60 patients included in the comparative analysis stratified by type of anaesthesia technique duringopen radical cystectomy

Variables	Study group (n = 15)	Control group (n = 45)	p value
Median (IQR) oxygen saturation percentage in holding area	98% (98–99%)	99% (97–99%)	0.12
Median (IQR) pain VAS score 24 h after surgery	0 (0–1)	2 (1–2.5)	<0.001
Compliance to ERAS protocol (n, %)	15 (100%)	39 (86.7%)	0.13
Nasogastric tube placement (n, %)	2 (13.3%)	7 (15.6%)	0.83
Median (IQR) time to oral diet intake (days)	1 (1–1)	1 (1–1)	0.47
Median (IQR) time to resumption of bowel sounds (days)	2 (2–3)	2 (2–3)	0.63
Median (IQR) time to flatus passage (days)	2 (2–3)	2 (2–3)	0.51
Median (IQR) time to stool passage (days)	5 (3–6)	5 (4–6)	0.39
Median (IQR) time to ambulation (days)	3 (3–4)	3 (3–4)	0.45

Abbreviations: ERAS, Enhanced Recovery after Surgery; IQR, interquartile range; VAS, visual analogue scale.

Rescue medication within the first 24 h was required by no patients in the study versus three (6.7%) patients in the control group (time to first rescue medication: 3, 6 and 10 h, respectively). Rescue medication between POD 1 and 4 was required by 1 (6.7%) patient in the study (time to first rescue medication: 24 h) versus four (8.9%) patients in the control group (time to first rescue medication: 8, 20, 38 and 48 h, respectively). All these patients only required a single dose of rescue medication as per protocol.
Compliance to ERAS protocol was observed in 15/15 (100%) patients in the study and in 39/45 (86.7%) patients in the control group (p = 0.13). Reasons for protocol non-compliance were failure of mobilisation on POD 1 and delayed start of solid oral diet beyond POD 2 in four and two patients, respectively.
However, no significant differences between the two groups were detected with regard to return to oral diet, bowel function recovery and time to ambulation (Table 3). Median LOS was 12 days (IQR 10–16) in the study and 14 days (IQR 11–17) in the control group (p = 0.46). Rate of 90-day postoperative complications was comparable in the two groups (p = 0.76). In detail, minor complications were detected in five (33.3%) patients in the study and in 14 (31.1%) patients in the control group. Major complications were observed in two (13.3%) patients in the study and in five (11.1%) patients in the control group, including one fatal event because of acute myocardial infarction on POD 65. Specifically, no SpEA-related complications (such as epidural hematoma or other bleeding complication) were recorded. [49]

Laboratory tests subanalyses

eGFR values

Considering the overall cases included in the study, the median (IQR) values of preoperative, post-operative and final eGFR were 69.2 (37.5-84.2), 52.9 (35.6-69.5), and 72.2 (48.5-89.8) ml/min x 1.73 m^2 ($p<0.001$). The median value of the Δ between preoperative and post-operative values was -6.6 (-14.8 – 0.97) and the differences statistically significant ($p<0.001$).
According to the type of anesthesia, the median (IQR) preop eGFR value was 83.3 (56-87.5) in the study group and 58.9 (34.3-78.8) in the control ones ($p=0.02$). The median (IQR) postop eGFR was 66.3 (37.5-91.8) in the study group and 44.9 (35.4-62.6) in the control ones ($p=0.01$). The median final eGFR value in the SpEA group was 89.8 (49.4-98.5) versus 68.7 (43.2-84.4) in the general anesthesia group ($p=0.03$). Interestingly, no differences were observed in the median Δ values calculated in the two groups between preop and postop eGFR values ($p=0.12$) and between preop and final values ($p=0.76$).

Neutrophil/lymphocyte ratio

Considering the overall cases included in the study, the median (IQR) values of preoperative, post-operative and final N/L ratio were 2.8 (2.1-4), 12.1 (8.4-15.9), and 3.7 (2.5-5.5) ($p<0.001$). The median (IQR) value of the Δ between preoperative and post-operative values was +8.5 (+5 - +11.7) and the difference was statistically significant ($p<0.001$). The median value of the Δ between preoperative and final values was +0.8 (+0.06 - +2) and the difference was statistically significant ($p<0.001$).
According to the type of anesthesia, the median (IQR) preop N/L ratio was 2.9 (2.1-4.8) in the study group and 2.8 (2.1-3.8) in the control ones ($p=0.60$). The median (IQR) postop N/L ratio was 10.8 (8.3-15.6) in the study group and 12.2 (8.4-16.8) in the control ones ($p=0.91$). The median final N/L ratio in the SpEA group was 3.7 (3 – 5.3) versus 3.6 (2.3-5.5) in the general anesthesia group ($p=0.44$). Interestingly, no

differences were observed in the median Δ values calculated in the two groups between preop and postop eGFR values (p=0.81) and between preop and final values (p=0.63).

Platelet/lymphocyte ratio

Considering the overall cases included in the study, the median (IQR) values of preoperative, post-operative and final P/L ratio were 148.9 (119.2-206.5), 233.1 (159.8-335.5), and 215.3 (160-286), respectively (p<0.001). The median (IQR) value of the Δ between preoperative and post-operative values was +79.5 (+19.5% - +155.4%) and the difference was statistically significant (p<0.001). The median value of the Δ between preoperative and final values was +63.2 (+4 - +99.6%) and the difference was statistically significant (p<0.001).
According to the type of anesthesia, the median (IQR) preop P/L ratio was 145 (99.3-213.4) in the study group and 150 (123.5-198.6%) in the control ones (p=0.65). The median (IQR) postop P/L ratio was 242 (161-428) in the study group and 227 (157.6-329.2) in the control ones (p=0.28). The median final P/L ratio in the SpEA group was 285 (190.1-316.1) versus 209.9 (155.5-270.3) in the general anesthesia group (p=0.09). Interestingly, no differences were observed in the median Δ values calculated in the two groups between preop and postop eGFR values (p=0.07) and between preop and final values (p=0.21).

Discussion

Our comparative study showed that SpEA is feasible, safe and effective in patients undergoing ORC. No significant differences were observed between SpEA and GA in terms of perioperative parameters, except for shorter anaesthesia time and greater early pain control with SpEA.
According to the Literature, evaluated laboratory parameters were not influenced by the different type of anesthesia used in this series of patients who underwent radical cystectomy and urinary diversion. Therefore, other laboratory parameters should be tested to eventually identify, if present, any difference between combined spinal/epidural and general anesthesia.

Whereas several endoscopic procedures in the lower and upper urinary tract are usually performed under loco-regional anaesthesia, the routine use of spinal and/or epidural anaesthesia for oncological interventions in the pelvis or lower abdomen is exceptional. SpEA combines the advantages of spinal anaesthesia, with a rapid starting effect and limited effect on good motor blockade, with those of epidural analgesia, which enables an optimal postoperative pain control. [33] [35] SpEA may position itself as a viable alternative to standard GA, being particularly attractive for certain categories of patients. For instance, in current practice, a substantial proportion of RC candidates are elderly and have multiple relevant comorbidities. In these patients, the use of SpEA instead of traditional GA might reduce cardiovascular and respiratory stress, thus abolishing the need for postoperative intensive or semi-intensive monitoring and care, and decrease the risk of cardiopulmonary complications and neurological disorders. Very few non-comparative studies have investigated the role of loco-regional anaesthesia in patients undergoing ORC. In 2013, Friedrich-Freksa et al. [26] were the first to report on a case series of 28 patients receiving SpEA.18 In the same year, Karl et al. [25] reported their experience with spinal and/or epidural anaesthesia in a smaller series of nine ORC cases.19 In 2015, Tzortzis et al. [53] published a retrospective analysis of 18 octogenarians with ASA score ≥3 who underwent ORC under SpEA.20 Finally, in 2017, Gerullis et al. [54]reviewed the literature adding three further cases performed under epidural anaesthesia only. Overall, ORC under loco-regional anaesthesia was proved to be feasible, and no specific complications or safety issues were observed. However, it should still be considered in a development stage according to the IDEAL criteria. Our study is a step forward towards its clinical evaluation, being the first exploratory, controlled study comparing SpEA with standard of care GA. Virtually all intraoperative and postoperative parameters were comparable with the two anaesthesia techniques, which is particularly reassuring considering that our population includes mostly elderly and comorbid patients. The only two significant differences were in favour of SpEA. First, median anaesthesia time was shorter by 40 min, which might be viewed as a valuable aid to the rationalization of operating room resources, although an ad hoc cost analysis would be needed to fully assess its effect. Second, SpEA was associated with a significantly greater pain reduction in the early postoperative pe compared with GA. This finding could represent a great advantage of the loco-regional technique, which could benefit even younger and fitter RC candidates. Side effects of SpEA could be hypotension, bradycardia, cardiac arrhythmia, cerebral

ischemia, cardiac arrest in rare cases, respiratory insufficiency due to high spinal anaesthesia, paraplegia because of epidural haematoma or abscess, motor blockade, nausea and vomiting, pruritus and postdural puncture headache. [36] Notably, we observed none of them, thus confirming the safety of this anaesthesia technique applied to RC. We acknowledge the following limitations to the present study. First, the study group included only a limited number of patients. This was deliberately decided in view of the exploratory study design. Second, we have reported the experience of a single high-volume surgeon and two dedicated expert anaesthesiologists working at an academic tertiary referral institution. Our promising findings should, then, be confirmed by studies including multiple surgeons and anaesthesiologists. Third, only a single pain assessment in the early postoperative period was performed. However, we believe there would have been no differences at later time points since the epidural catheter was no longer in place.

We also mention the case of a patient who underwent laparoscopic sigmoid resection for cancer, where we decided to apply the locoregional technique due to the severity of the lung pathology.

The patient was a former bricklayer, suffering from severe obstructive syndrome, with the presence of widespread expiratory groans throughout the lungs upon auscultation of the chest, on home O2 therapy and on therapy with cortisone and inhaled beta 2 agonists. In agreement with the surgeon colleague, we worked at intra-abdominal pressures between 8 and 10 mmHg, for a total duration of the entire procedure of 3 hours and 30 minutes.

The same intra- and post-operative protocol was used as for radical cystectomies, but during the initial phase, midazolam 2mg and fentanest 50 gamma IV were administered to help manage pain in the right shoulder after pneumoperitoneum induction.

Epidural catheter removal and mobilization were done 24 hours after surgery. Two doses of paracetamol 1000mg/day were given for post-operative pain, with a VAS score of less than 3 and a length of stay of 10 days after catheter removal.

All patients were monitored non-invasively for HR, NIBP, SpO2, and BIS to evaluate sedation levels and minimize dexmedetomidine-related hemodynamic effects. The initial dosage was 0.7 mcg/kg/h, with adjustments of +/- 0.1-0.2 mcg/kg/h as a maintenance dose for the entire duration of the intervention. The doses were decreased in the last surgical time, while maintaining BIS values between 65-55. All patients were sedated but still responsive to verbal stimulation and breathing spontaneously.

CONCLUSIONS

In conclusion, our exploratory, controlled study confirmed the feasibility, safety and effectiveness of a pure loco-regional anaesthesia in patients undergoing ORC.
These techniques have minimal hemodynamic impact and do not affect the patient's respiratory profile, leading to faster recovery and fewer complications. Similar intra- and postoperative outcomes were observed when compared with current standard of care, GA. Of note, SpEA was associated with a significantly shorter anaesthesia time and greater pain reduction in the early postoperative period compared with GA. Our preliminary data warrant further exploration in larger multi-surgeon and multi-anaesthesiologist comparative studies. SpEA seems particularly suited for those RC candidates who are elderly or have multiple relevant comorbidities increasing their anaesthesiology risk for GA.
According to the Literature, laboratory parameters were not influenced by the different type of anesthesia used in this series of patients who underwent radical cystectomy and urinary diversion. Therefore, other laboratory parameters should be tested to eventually identify, if present, any difference between combined spinal/epidural and general anesthesia.
Furthermore, the use of dexmedetomidine is beneficial because it allows for rapid sedation elimination in line with the ERAS protocol and reduces the dosage of local anesthetic.

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