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Ninety Days complications rate in patients undergoing radical cystectomy with enhanced recovery protocol

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Abstract

Bladder cancer is a carcinoma of the urothelial, or "umbrella," cells that line the lumen of the urinary bladder. Technically, urothelial carcinoma includes tumors of the bladder, upper urinary tract (renal pelvis and ureters), and proximal urethra. Bladder cancer accounts for approximately 90% to 95% of urothelial carcinoma; bladder cancer comprises 75% pure urothelial carcinoma and 25% "variant" histology, adding complexity to the management of this disease. Bladder cancer can be categorized in several way, almost all bladder cancers originate in the urothelium, which is a 3- to 7-cell mucosal layer within the muscular bladder. Squamous cell carcinoma of the bladder can involve multiple sites; however, the lateral wall and trigone are more commonly involved by this tumor. All small cell carcinomas of the urinary system identified so far have been located in the urinary bladder, most commonly in the dome and vesical lateral wall. Radical cystectomy is a crucial surgical technique in managing MIBC, high-risk NMIBC, and treatment-refractory NMIBC. Despite a high perioperative mortality rate (5-10%), it now carries a 1-2% mortality rate due to improvements in surgical technique, intensive care medicine evolution, and antibiotic availability.

Keywords: Ninety Days complications rate, Radical cystectomy, Recovery

Full length article **Corresponding Author*, e-mail: drshehabemad88@gmail.com Doi # https://doi.org/10.62877/6-IJCBS-24-25-19-6

1. Introduction

The bladder is a muscular urine reservoir located behind the pubis symphysis in the pelvis. It is connected to the umbilicus by the median umbilical ligament, representing the obliterated urachus. Urine from the kidney enters the bladder at the trigone, with intravesical ureteral orifices forming the trigone's superolateral borders [1]. Bladder cancer is a type of urothelial carcinoma, affecting the bladder, upper urinary tract, and proximal urethra. It accounts for 90%-95% of urothelial carcinoma, with 75% pure and 25% variant histology, complicating management. Bladder cancer can be categorized in various ways [2]. Bladder cancer is staged using the International Union against Cancer and the American Joint Committee on Cancer Staging's tumor, node, and metastasis (TNM) system [3]. Patients with low-risk disease undergo initial resection with cystoscopic surveillance. High-grade stage Ta or T1 disease requires repeat resection due to under-staged or persistent disease. Intermediate-risk and high-risk patients receive intravesical therapy unless upstaging to muscle-invasive disease occurs on repeat resection [4,5] . The aim of this study was to show the efficacy of enhanced recovery after surgery protocol in management of patients undergoing radical cystectomy for bladder cancer with intestinal incorporation in urinary diversion and to compare the complication rate of this protocol to the standard one.

2. Anatomy of the bladder

The bladder is a muscular urine reservoir located behind the pubis symphysis in the pelvis. It is connected to the umbilicus by the median umbilical ligament, representing the obliterated urachus. Urine from the kidney enters the bladder at the trigone, with intravesical ureteral orifices forming the trigone's superolateral borders [1]. Most bladder cancers originate in the urothelium, a mucosal layer within the muscular bladder. Squamous cell carcinomas often involve the lateral wall and trigone, while all small cell carcinomas of the urinary system are found in the bladder, primarily in the dome and vesical lateral wall [6].

3. Epidemiology of bladder cancer

Urothelial carcinoma of the bladder (UCB) is the fourth most common cancer in men and the fifth most common overall, with approximately 80,470 new cases and 17,670 deaths expected in 2019 [8]. In Africa, the highest incidence of SCC has been seen in schistosomal-endemic areas, notably Sudan and Egypt, where SCC ranges from two thirds to three quarters of all malignant tumors of the bladder. In recent years, a few studies from Egypt have shown a reversal of this trend due to the better control of schistosomiasis in the region, whereas in other parts of Africa the association is unchanged [9,10].

3.1. Etiology and risk factors

Cigarette smoking, occupational exposures like benzene dyes, and chronic inflammatory conditions increase the risk of bladder cancer. Pelvic radiation and cyclophosphamide also increase the risk. Schistosoma haematobium infection causes most bladder SCC cases, with 82% of patients harboring S. haematobium eggs in the bladder wall. Advanced age is the greatest risk factor, with an average diagnosis between 70-84 years. Men are diagnosed with bladder cancer 3-4 times more frequently than women, attributed to exposures and lifestyle. Stasis of urine-containing carcinogens in men with prostatic enlargement and urinary retention may also increase the risk [11,12]. The most studied genes linked to bladder cancer are N-acetyltransferase 2 (NAT2) and a deletion of glutathione S-transferase μ (GSTM1). These genes are involved in the metabolism of aromatic amines, affecting individuals exposed to environmental carcinogens, such as cigarette smoke [13,15].

3.2. Hereditary

Among other tumors that may develop in patients with Lynch syndrome, the lifetime risk of urothelial tumors of the upper urinary tract is estimated to be 0.4% to 20% Whether the risk of bladder cancer is increased, however, remains controversial [16].

4. Pathophysiology and Molecular Biology

Bladder cancer is a type of urothelial carcinoma, affecting the bladder, upper urinary tract, and proximal urethra. It accounts for 90%-95% of urothelial carcinoma, with 75% pure and 25% variant histology, complicating management. Bladder cancer can be categorized in various ways [2]. Low-grade papillary non-muscle-invasive BC can progress to muscle-invasive BC as a result of gaining CDKN2A loss. Muscle-invasive BC arises from flat dysplasia or carcinoma in situ (CIS); the lesions show TP53 mutations and LOH of chromosome 9. The invasive carcinoma can then further gain RB1 and PTEN loss along with other alterations acquiring metastatic potential. Overall, non-muscle-invasive BC usually show diploid or near-diploid karyotypes and fewer copy number alterations compared to muscle-invasive BC. Muscle-invasive BC is usually aneuploid, with numerous chromosomal alterations [17].

5. Histopathology

5.1. Urothelial carcinoma

Urothelial carcinoma (UC) is a type of cancer originating from stem cells near the basement membrane of the epithelial surface. Its molecular pathology varies depending on genetic alterations [18]. The most common path involves a papillary tumor that invades the bladder lumen and can metastasize [19]. However, 10% of UCs, or CIS, have a noninvasive, high-grade UC that spreads along the bladder's surface and may eventually progress to an invasive form [20]. Transitional cell carcinoma of the bladder can be low-grade or high-grade, with low-grade cancer rarely recurring after treatment and rarely causing death [21]. High-grade bladder cancer is more aggressively treated and more likely to result in death [37]. Bladder cancer is divided into MIBC and NMIBC based on invasion of the muscularis propria, a thick muscle deep in the bladder wall [23]. In the United States, transitional cell carcinomas represent over 90% of bladder cancers. In Egypt, transitional cell carcinoma has increased from 20% to 66%, while squamous cell carcinoma has decreased from 73% to 25% in the past decade [24].

5.2. Squamous cell carcinoma (SCC)

It is a malignant neoplasm originating from bladder urothelium, with a pure squamous phenotype. It is similar to other organ-specific squamous cell tumors. Diagnosis should only be made when the tumor is solely composed of squamous cell components, without conventional urothelial carcinoma components [25].

5.3. Adenocarcinomas

Adenocarcinomas can be primary or secondary, arising from bladder urothelium, distant metastasis, or direct extension from other organs. Although urachal adenocarcinomas are not anatomically related to the urinary bladder, they share similar pathologic and clinical features.

5.4. Small cell carcinomas

Small cell carcinoma is a rare, poorly differentiated neuroendocrine neoplasm primarily found in the lung but can also occur in extrapulmonary sites like the prostate and bladder, causing paraneoplastic syndromes [26].

6. Clinical course

Bladder cancer has a diverse clinical course, with low-grade superficial cases having minimal risk of progression. High-grade non-muscle-invasive cancers often progress, and muscle-invasive cancers are often lethal [27]. Painless gross hematuria is the classic presentation, with cytoscopy, cytology, and biopsy being the primary diagnostic tests [28].

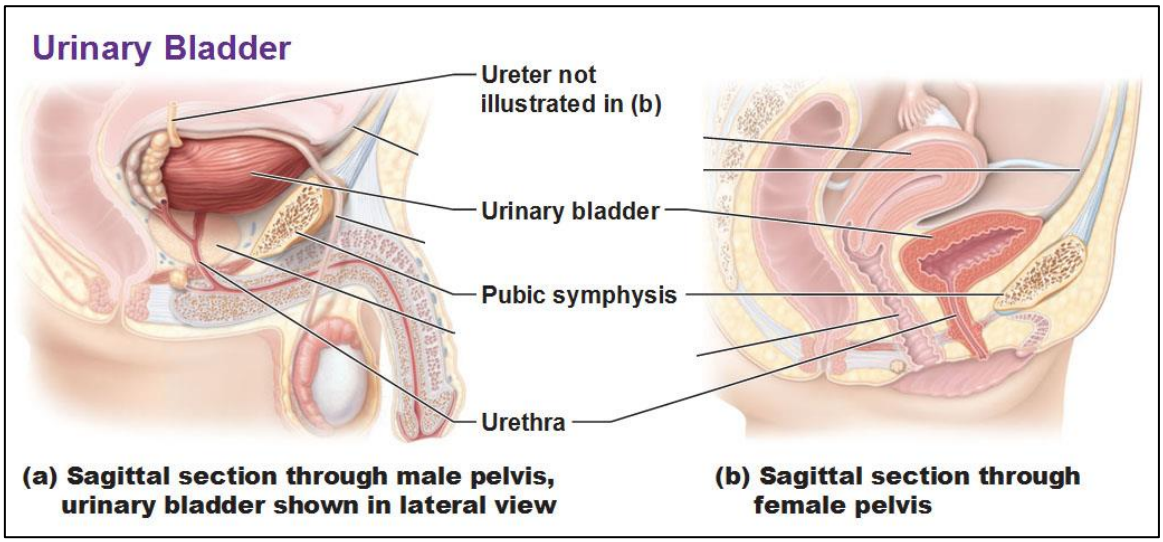

Figure 1. Anatomy of the male and female urinary bladder, sagittal view [7]

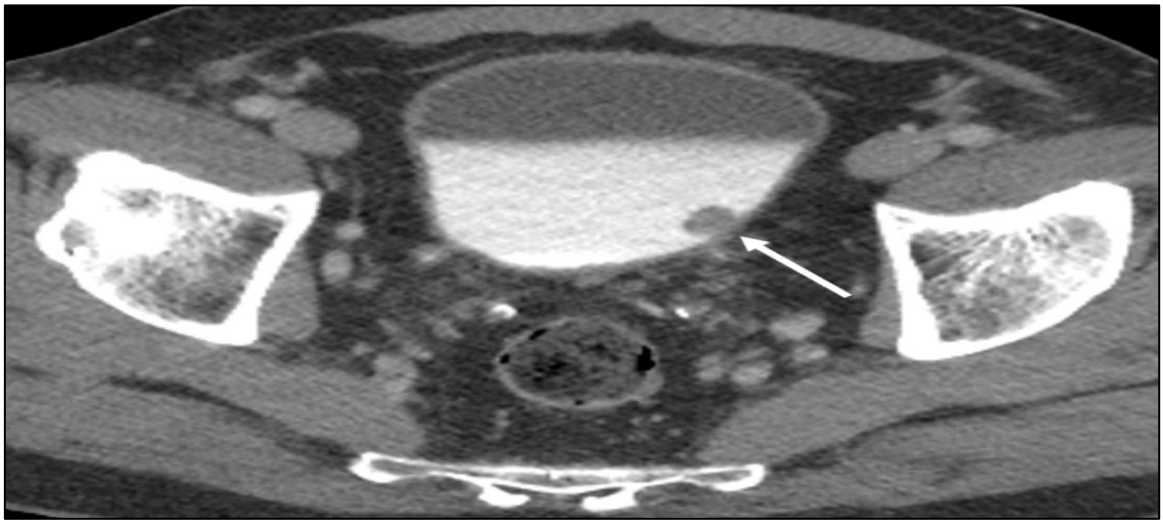

Figure 2. Axial CT images from the excretory phase of a CT urogram performed for hematuria demonstrating a polypoid filling defect arising near the left ureteral orifice (arrow), highly suspicious for bladder cancer [34]

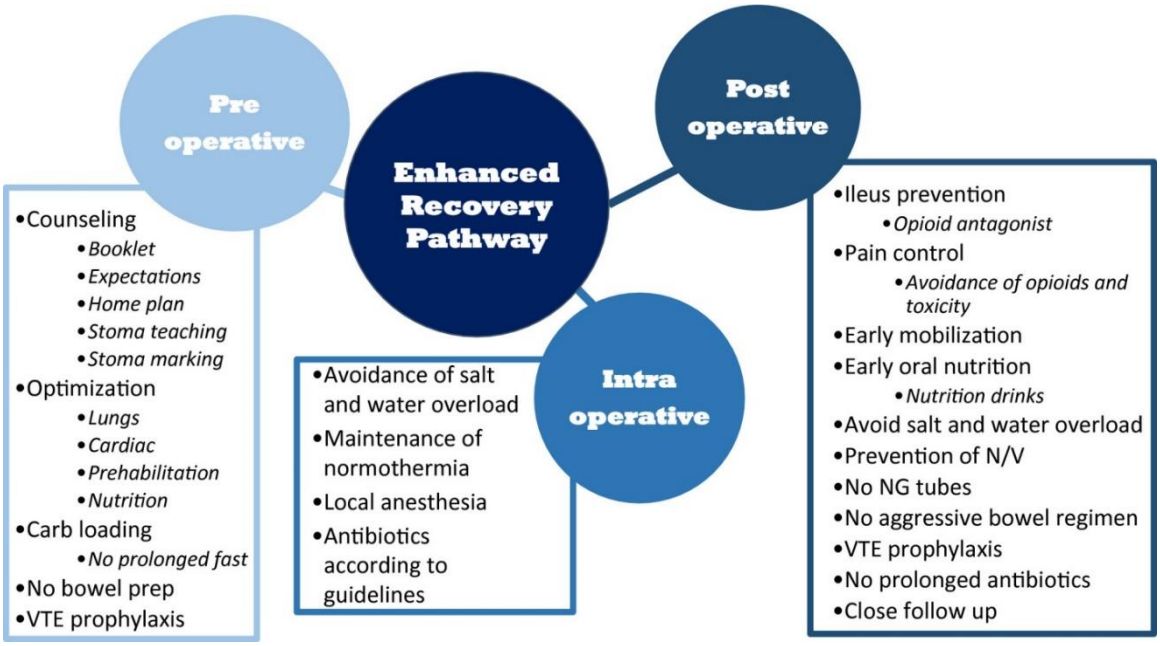

Figure 3. Preoperative, intraoperative, and postoperative components of Enhanced Recovery after Surgery (ERAS) [62]

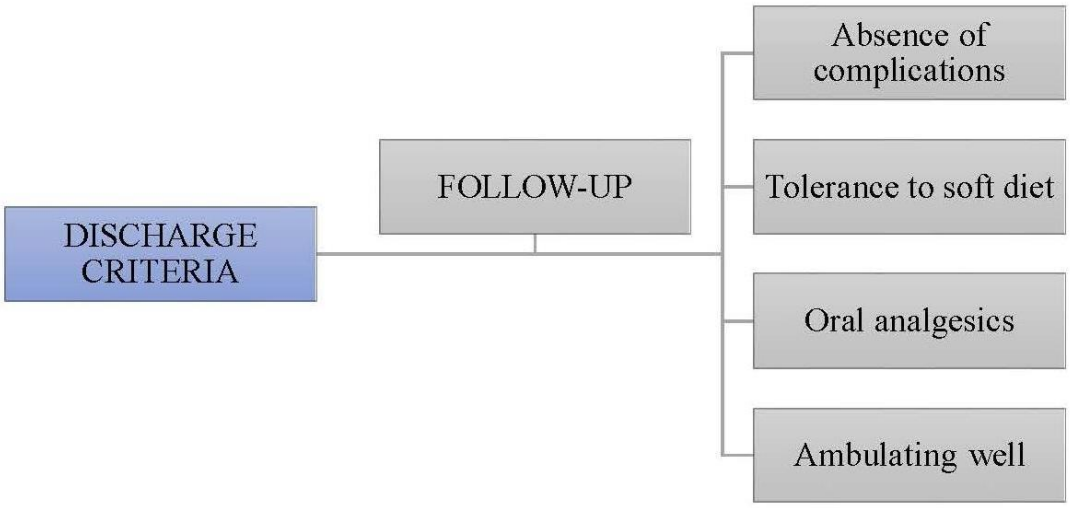

Figure 4. Enhanced Recovery after Surgery (ERAS): discharge criteria [73]

7. Diagnosis

The diagnosis of bladder cancer involves various methods, [29] including urinary cytology, urinary tract imaging, cystoscopy, and histologic examination of specimens obtained by transurethral resection of the bladder tumor (TURBT) [30]. For muscle-invasive bladder cancer (MIBC), [31] EUA guidelines recommend using computed tomography (CT) for staging, CT urography for upper tract evaluation, and magnetic resonance urography for staging locally advanced or metastatic disease. CT and MRI are generally equivalent for diagnosing local disease and distant metastases in the abdomen. Novel molecular and genetic markers have been studied for urothelial diagnosis, but they have not been proven to replace urine cytology and cystoscopy [32]. Urinary tumor markers can be used in addition to cystoscopy and cytology in patients undergoing surveillance for bladder cancer [33].

8. Staging

Bladder cancer is staged using the International Union against Cancer and the American Joint Committee on Cancer Staging's tumor, node, and metastasis (TNM) system [3].

9. Management

9.1. Non–Muscle-Invasive Bladder Cancer

Patients with low-risk disease undergo initial resection with cystoscopic surveillance. High-grade stage Ta or T1 disease requires repeat resection due to under-staged or persistent disease in 17%-67% of Ta tumors and 20%-71% of T1 tumors. Intermediate-risk and high-risk patients should receive repeat resection [5-4].

9.2. Intravesical Therapy

Intravesical chemotherapy can be administered within 24 hours of TURBT to treat low- or intermediate-risk disease, killing free-floating tumor cells and preventing urothelium seeding [35].

9.3. Bacille Calmette-Guérin

Bacille Calmette-Guérin (BCG), a live attenuated form of Mycobacterium bovis, is the preferred treatment for high-risk NMIBC and intermediate-risk NMIBC. Its effects are complex, as it adheres to the urothelium, induces innate and adaptive immune responses [36].

9.4. Muscle-Invasive Bladder Cancer

MIBC patients undergo neoadjuvant therapy, radical cystectomy, pelvic lymph node dissection, urinary diversion, or a bladder-sparing protocol like chemo radiation or partial cystectomy in selected cases [37].

9.5. Radical Cystectomy, Pelvic Lymph Node Dissection, and Urinary Diversion

Radical cystectomy involves removing various parts of the body, including the bladder, prostate, and uterus, and removing lymph nodes. This procedure is crucial for curative-intent cystectomy and is supported by the AUA, EAU, and NCCN. Lymph node dissection can provide prognostic information and guide adjuvant therapy, as up to 25% and 8% of patients with MIBC and high-risk NMIBC may harbor lymph node metastases [38].

9.6. Bladder-Sparing Approaches

Trimodal therapy (TMT) is a combination of maximal TURBT, radio-sensitizing chemotherapy, and radiation, used as an alternative to cystectomy for patients who decline or are ill-suited for surgery [31]. TMT chemotherapy, often combining cisplatin with fluorouracil or paclitaxel, fluorouracil with mitomycin C, or cisplatin-alone or low-dose gemcitabine, serves as a radio-sensitizing agent and systemic treatment for micro-metastatic diseases [40-39].

9.7. Advanced and Metastatic Disease

Only 4% of bladder cancer patients have metastatic disease, with poor prognosis and median survival of 13-15 months. Advances in treatment include immunotherapy, targeted therapy, and antibody-drug conjugates, especially for patients with poor performance or renal dysfunction [41].

9.8. Adjuvant Therapy

The role of adjuvant chemotherapy in patients with adverse pathologic features such as extra-vesical extension or node-positive disease after cystectomy remains controversial because prospective data do not support its use [42].

10. Radical cystectomy and Its Complications

Radical cystectomy is a crucial surgical technique in managing MIBC, high-risk NMIBC, and treatment-refractory NMIBC [43]. Despite a high perioperative mortality rate (5-10%), it now carries a 1-2% mortality rate due to improvements in surgical technique, intensive care medicine evolution, and antibiotic availability [44].

10.1. Indications

Radical cystectomy is recommended for muscle-invasive bladder cancer without metastasis, superficial bladder tumors resistant to cystoscopic resection, extensive disease, invasive prostatic involvement, stage-pT1 grade-3 tumors unresponsive to BCG vaccine therapy, CIS refractory to immunotherapy or chemotherapy [45].

10.2. Contraindications

Contraindications to radical cystectomy include the following: [46] Bleeding diathesis. Evidence of gross,

unresectable metastatic disease (unless performed for palliation). Medical comorbidities that preclude operative intervention (eg, advanced heart disease, poor pulmonary mechanics, advanced age)

Pelvic lymph node dissection (PLND)

Radical cystectomy is recommended for muscle-invasive bladder cancer without metastasis, superficial bladder tumors resistant to cystoscopic resection, extensive disease, invasive prostatic involvement, stage-pT1 grade-3 tumors unresponsive to BCG vaccine therapy, CIS refractory to immunotherapy or chemotherapy.

Urinary diversion

Urinary diversion is a necessary component of RC. Two general categories of diversion can be distinguished: incontinent and continent diversion [47].

10.3. Complications of RC

Morbidity and mortality

RC is associated with relatively high perioperative morbidity and mortality, despite improvements in surgical techniques and perioperative care. The incidence of complications after surgery has been reported to be in the range of 30–70% [48].

Early Complications

Open radical cystectomy is a common surgery resulting in gastrointestinal (29%), infection (25%), and wound-related complications (15%) complications. Factors such as age, prior abdominal or pelvic surgery, ASA > 2, and estimated blood loss can predict high-grade complications. Urinary leakage is more common in the early postoperative period, and stents of the ureteroileal anastomosis can help prevent this. Urinary leaks can be managed conservatively, but a cystogram is typically performed at three weeks to check for orthotopic bladder substitute (OBS) leaks. Infection is the second most common perioperative complication, and prophylactic antibiotics are prescribed to reduce infection. Wound-related complications are more common in open cystectomy, and deep vein thrombosis (DVT) is a serious postoperative complication affecting up to 4.7% of patients [49,50]**.**

Late Complications

Urinary Tract Infection: The presence of leucocytes and bacteria is commonly seen in urine culture of patients with OBS [51]**,** Deterioration in Renal Function: There are two main factors following OBS that are thought to play a role in deterioration of patients' renal function: Hydronephrosis secondary to ureteroileal strictures. Reflux of infected urine. High-pressure reflux of infected urine can cause renal function deterioration over time [52].

Calculi Formation: The majority of stones can be managed via an endoscopic approach although percutaneous and laparoscopic approaches are sometimes necessary [53], Metabolic Complications, Incontinence

Urinary Retention**:** The main risk factors for urinary retention after OBS reconstruction are a large capacity OBS due to excessive bowel segment length and non- nerve sparing techniques [54].

10.4. Standard protocol in preoperative preparation for radical cystectomy

Urology textbooks recommend routine mechanical bowel preparation before cystectomy and urinary diversion. Early studies showed that unprepared bowels increased wound infection rates, intraperitoneal abscesses, and anastomotic dehiscence. Mechanical preparation resulted in collapsed bowels during surgery, reducing leaks. The practice dates back to the 1970s and is beneficial for elective intestinal surgery. [55,56].

Mechanical bowel preparation

Bowel preparation involves mechanical and antibiotic methods to reduce complications from intestinal surgery. Mechanical preparation reduces fecal count and bacteria, while antibiotic preparation decreases bacterial count per gram of feces. Conventional preparations often exhaust patients and cause nutritional depletion. Whole-gut irrigation, which involves placing a nasogastric tube into the stomach and infusing fluids with mannitol, has been used to reduce fecal burden before surgery. Oral cathartic bowel preparation, using magnesium citrate or sodium phosphate, is also effective [57,58]. Bowel preparation can cause metabolic complications and electrolyte disturbances, potentially impacting surgical care, especially in elderly and debilitated patients, as sodium phosphate preparation can disrupt potassium, calcium, and phosphorus levels [59].

Antibiotic bowel preparation

Common antibiotics used for bowel preparation include kanamycin, neomycin and erythromycin base, and neomycin and metronidazole. They reduce septic complication rates and wound infection rates [60].

10.5. Enhanced Recovery protocols after radical cystectomy

ERAS programs, also known as fast track protocols, are evidence-based strategies that standardize and enhance perioperative medical care. The ERAS protocol, established in elective and non-GI surgical procedures, has been well established in gastrointestinal and non-GI procedures, but not as well established in emergency surgery [61].

Preoperative Components of ERAS

The body goes into a catabolic state during surgery, as various stress hormones and inflammatory mediators are released in response to stress, which in turn leads to insulin resistance [61]. The conventional ERAS protocol includes preoperative components like preadmission counseling,

fluid and carbohydrate loading, no prolonged fasting, selective bowel preparation, antibiotic prophylaxis, thromboprophylaxis, non-opioid analgesics, and no premedication [63]. Preadmission counseling is crucial in emergency preoperative settings, involving patient, caregivers, and family members. It's essential to discuss the procedure's nature, potential complications, and expected hospital stay. Pre-warming fluids 2 hours before and after surgery is recommended to reduce postoperative complications like infections, as it is proven to be effective [64]. Carbohydrate loading and selective bowel preparation in elective settings may not be feasible in emergency settings, but can reduce postoperative symptoms like thirst, hunger, anxiety, insulin resistance, and protein loss. Standard mechanical bowel preparation is avoided in ERAS protocols due to potential dehydration, fluid imbalances, and spillage risks, requiring selective preparation when necessary. Opioid analgesia can, however, be used as a component of multimodal analgesia for breakthrough pain, as was the case in a study of ERAS in perforated duodenal ulcer. Nasogastric (NG) tube placement at the time of admission, along with IV fluids, antibiotics, and antacids, was used as part of preoperative care. These studies suggest that most of the preoperative components of ERAS—such as preadmission counseling, goal-directed fluid therapy (GDFT), non-opioid analgesics for pain management, antibiotic prophylaxis, and thromboprophylaxis—are indeed feasible in the setting of emergency abdominal surgery [65].

Intraoperative Components of ERAS

Surgical stress triggers metabolic changes, endocrine and inflammatory responses, affecting the body's homeostasis. An ERAS protocol aims to reduce injury and stress, focusing on intraoperative care components like short-acting anesthetic agents, GDFT, normothermia, and minimal-access surgery [63].

Control of pain

ERAS involves managing surgical pain, reducing complications, and using multimodal analgesia to relieve pain, enhance enteral feeding, encourage mobilization, and reduce opioid side effects for quicker recovery [66]. Multimodal analgesia consists of thoracic epidural analgesics and NSAIDs, but due to concerns about bowel anastomoses, TAP blocks, spinal anesthesia, and IV lidocaine are preferred [67].

Maintenance of fluid volume and core temperature

Monitoring volume status using invasive, minimally invasive, and noninvasive techniques ensures euvolemia by tracking pulse rate, arterial blood pressure, urine output, CVP, CO2, stroke volume, and cardiac output. Urine output, while used to measure volume status, is influenced by factors like prerenal depletion and postrenal obstruction, making it a limited measure [68].

11. Commonly used techniques for assessing volume status include the following:

11.1. Use of minimal-access surgery

Smaller incisions in open surgical procedures reduce trauma and intraoperative bleeding. Laparoscopic surgery is a better approach, requiring smaller incisions and less tissue damage. However, prolonged operations may create a pneumoperitoneum, which can be counteracted with special ports and neuromuscular blocks. A coordinated effort from surgeons, anesthesiologists, and caregivers is crucial for successful postoperative outcomes [69].

12. Postoperative Components of ERAS

Postoperative ERAS implementation relies on patient care, including pain management, early removal of tubes, catheters, and drains, and early enteral feeding. ERAS pathways aim to reduce postoperative fatigue by promoting early mobilization, including removal of tubes, catheters, and drains. Incentive spirometry is performed to prevent atelectasis, and prophylactic antithrombotic agents are administered. Early enteral feeding prevents muscle wasting and fatigue, and can be started at the first bowel sounds or flatus [70].

13. Discharge and follow-up

An ERAS protocol enhances patients' recovery, preparing them for early discharge. Criteria include hospital admission, solid diet tolerance, pain control, and independent mobilization. No fixed protocol yet established [71]. Post-discharge follow-up evaluates complications and readmission rates, allowing for necessary protocol improvements. Patients can be prescribed oral analgesics and anti-secretory PPI therapy, with effective preoperative and postoperative counseling reducing readmission rates [72].

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