The Role of Exenterative Surgery in Advanced Urological Neoplasms

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Key Words
Advanced pelvic malignancies • Pelvic exenteration • Bladder cancer • Prostate cancer • Surgical outcomes

Abstract
Pelvic exenterative surgery is both complex and challenging, especially in the setting of locally recurrent disease. In recent decades, improved surgical techniques have facilitated more extensive resection of both locally advanced and recurrent pelvic malignancies, but its role in urological cancer surgery is highly selective. However, it remains an important part of the armamentarium for the management of bladder and prostate cancer cases where there is local invasion into adjacent organs or localized recurrence. Better diagnostics, reconstructive options and centralized care have reduced associated morbidity considerably, and it is still used rarely in palliative settings. Despite this, there is sparse prospective evidence reporting on long-term oncological or quality of life outcomes.

Introduction
Pelvic exenteration was first described as a potential palliative surgical intervention for locally advanced and recurrent gynecological malignancies [1]. Initial studies reported perioperative mortality rates exceeding 20%, with no patient surviving past 5-years [2]. Improvements in both perioperative care and surgical techniques have facilitated it being performed more routinely with curative intent. In select patients, pelvic exenteration is performed for locally advanced or recurrent pelvic malignancies, with acceptable morbidity and mortality [3]. The fundamental goal of exenterative surgery is to excise all locally advanced or recurrent disease while achieving clear margins [3]. This can involve the radical excision of adjacent organs or structures. Therefore good operative planning with radiological imaging and multidisciplinary input is needed [4].

In carefully selected patients, pelvic exenteration has acceptable surgical and oncological outcomes [5]. However, there is a paucity of information regarding quality of life (QoL) and patient-reported outcomes. This review outlines the current literature regarding the role of pelvic exenteration in locally advanced and recurrent urological malignancies, evaluating its associated surgical and survival outcomes.

Role in Urological Cancer

Although pelvic exenteration is a technically challenging operation, it is becoming increasingly feasible in locally advanced and recurrent urological cancers. Classical total pelvic exenteration involves the radical resection of the distal colon, rectum and anal canal. Additionally, both distal ureters, bladder, reproductive organs and adjacent lymph nodes are removed en-bloc [6]. With the removal of the bladder, urinary diversion is therefore required,
either by formation of an ileal conduit, wet colostomy or a neo-bladder [7]. Circumstances where the rectum is not involved and clear margins are attainable, anterior pelvic exenteration (APE) can be performed, sparing the excision of the anal canal, rectum and distal colon [8].

The most common form of radical surgery performed in urological malignancy is an APE in women and a radical cystoprostatectomy in men. Muscle invasive bladder cancer (MIBC) is the most common indication for radical pelvic surgery. Annually, 10,000 new cases of bladder cancer (BCa) are reported in the UK, representing 3% of all cancer cases [9]. Of these, approximately 1,500 will require APE/radical cystoprostatectomy for advanced disease [10, 11]. Locally advanced prostate cancer (PCa) often involves multi-modality treatment, commonly with radical surgery followed by adjuvant radiotherapy [12]. In addition, the modern era of surgery has placed increased emphasis on organ preservation and minimally invasive surgical options. Despite this, pelvic exenteration remains an important surgical modality in select cases of locally advanced or locally recurrent urothelial neoplasms [13]. Recently, robotic assisted procedures have become increasingly popular for complex pelvic surgery. Compared to the traditional laparoscopic resections, robotic surgery is thought to provide greater precision through improved dexterity and visualization. This results in potentially improved perioperative morbidity, decreased hospital length of stay, reduced pain and discomfort and faster recovery times for patients.

### Role of Pelvic Exenteration in BCa

Radical cystectomy and pelvic lymphadenectomy are the gold standard resections for MIBC and non-MIBC (NMIBC) failing previous treatment [14]. Cisplatin-based neoadjuvant chemotherapy should be used in all fit patients due to its known survival advantage [15]. Approximately, 75% of patients with BCa will present with NMIBC. The 5-year recurrence risk for these patients is 45% for those with high-risk tumors necessitating long-term surveillance [16].

Progression to muscle invasive disease confers a significantly worse prognosis and decreased cancer specific

### Table 1. Unadjusted postoperative outcomes after pelvic exenteration [18]

<table>
<thead>
<tr>
<th>Pre- or intra-operative variable</th>
<th>Total (n = 377)</th>
<th>Colorectal (n = 226)</th>
<th>Urologic (n = 151)</th>
<th>p</th>
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<tbody>
<tr>
<td>30 Day mortality, n (%)</td>
<td>5 (1.3)</td>
<td>2 (0.9%)</td>
<td>3 (2%)</td>
<td>0.393</td>
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<tr>
<td>Overall complication rate, n (%)</td>
<td>229 (60.7)</td>
<td>134 (59.3%)</td>
<td>95 (62.9%)</td>
<td>0.55</td>
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<td>Major complication rate, n (%)</td>
<td>188 (49.9)</td>
<td>104 (46%)</td>
<td>84 (55.6%)</td>
<td>0.085</td>
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<tr>
<td>Early return to the OR, n (%)</td>
<td>36 (9.5)</td>
<td>25 (11.1%)</td>
<td>11 (7.3%)</td>
<td>0.296</td>
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<tr>
<td>Length of stay, days</td>
<td>9.5 (7–15)</td>
<td>10 (8–17)</td>
<td>9 (7–12)</td>
<td>0.011</td>
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<tr>
<td>Operative time, minutes</td>
<td>414 (318–544)</td>
<td>470.5 (348.5–592.5)</td>
<td>366 (262–453.5)</td>
<td>&lt; 0.001</td>
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<td>Specific complications, n (%)</td>
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<tr>
<td>Superficial SSI</td>
<td>48 (12.7)</td>
<td>34 (15)</td>
<td>14 (9.3)</td>
<td>0.136</td>
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<tr>
<td>Deep SSI</td>
<td>11 (2.9)</td>
<td>11 (4.9)</td>
<td>0 (0)</td>
<td>0.004</td>
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<td>Organ space SSI</td>
<td>37 (9.8)</td>
<td>30 (13.3)</td>
<td>7 (4.6)</td>
<td>0.01</td>
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<td>Wound dehiscence</td>
<td>10 (2.7)</td>
<td>9 (4)</td>
<td>1 (0.7)</td>
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<td>Sepsis</td>
<td>40 (10.6)</td>
<td>31 (13.7)</td>
<td>9 (6)</td>
<td>0.026</td>
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<td>Septic shock</td>
<td>17 (4.5)</td>
<td>12 (5.3)</td>
<td>5 (3.3)</td>
<td>0.452</td>
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<td>Pneumonia</td>
<td>14 (3.7)</td>
<td>10 (4.4)</td>
<td>4 (2.6)</td>
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<td>Reintubation</td>
<td>13 (3.4)</td>
<td>8 (3.5)</td>
<td>5 (3.3)</td>
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<td>Prolonged vent. (&gt; 48 h)</td>
<td>22 (5.8)</td>
<td>18 (8)</td>
<td>4 (2.6)</td>
<td>0.042</td>
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<td>Pulmonary embolism</td>
<td>3 (0.8)</td>
<td>2 (0.9)</td>
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<td>Acute kidney injury</td>
<td>6 (1.6)</td>
<td>2 (0.9)</td>
<td>4 (2.6)</td>
<td>0.223</td>
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<td>Renal failure</td>
<td>4 (1.1)</td>
<td>2 (0.9)</td>
<td>2 (1.3)</td>
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<td>Urinary tract infection</td>
<td>40 (10.6)</td>
<td>28 (12.4)</td>
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<td>Stroke</td>
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<td>Cardiac arrest</td>
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<td>Myocardial infarction</td>
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<td>Postoperative bleeding</td>
<td>121 (32.1)</td>
<td>53 (23.5)</td>
<td>68 (45)</td>
<td>&lt; 0.001</td>
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<td>Deep venous thrombosis</td>
<td>14 (3.7)</td>
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SSI = Surgical site infections.
survival, therefore early radical resection should be offered to those patients with recurrent disease, high-risk NMIBC or those that have failed initial intravesical treatments [17]. The data regarding exenteration outcomes for BCa is largely retrospective, single-center and low-volume. The largest review to date by Speicher et al. [18] examined exenterative outcomes for both colorectal and bladder malignancies. Their study included over 1,400 patients, observing a 30-day mortality of < 2%, with good overall survival for locally advanced BCa (table 1).

The goal of MIBC treatment is to optimally balance oncologic outcomes with QoL for the patient. Radical cystectomy with bilateral pelvic lymphadenectomy remains the mainstay treatment for MIBC [19].

A large single-center study of 1,054 patients demonstrated recurrence-free survival and overall survival of 68 and 66% at 5 years and 60 and 43% at 10 years, respectively [20]. However, the 5-year recurrence-free survival in node-positive patients who underwent cystectomy was considerably less at 34–43% [21, 22]. APE performed at higher volume centers is associated with improved postoperative outcomes, decreased mortality, shorter length of hospital stay and lower re-admission rates [23].

In recent years, an increased focus on patient QoL has led to a renewed interest in minimally invasive surgery. Bladder sparing surgery may be undertaken in those with localized disease or in those unwilling to undergo radical cystectomy, although this is not recommended, as recurrence rates of 30% are reported [24].

### Role of Pelvic Exenteration in PCa

PCa is the second most common cancer in men in the UK with 46,700 new diagnoses in 2014, of which 11,300 deaths were directly attributable. The incidence of PCa is strongly age dependent with rates varying according to geographic region [25]. The lack of screening programs for PCa and the sporadic use of prostate specific antigen testing means detection rates vary [26].

#### Table 2. 30 Day mortality rates by hospital volume [23]

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aggressive patient education strategies and opportunistic screening strategies, patients still present with advanced localized and systemic disease [27].

Treatment strategies for PCa are based primarily on risk stratification models incorporating Tumor Node Metastasis classification, Gleason score, prostate specific antigen levels and patient co-morbidity index to determine the optimum management strategy [28]. However, despite this, the management of locally advanced PCa remains controversial [29]. The optimal management of locally advanced PCa incorporates multimodality management with surgery, radiotherapy and hormonal treatment [15]. Current guidelines are based on several large-scale randomized controlled trial’s and recommend radiotherapy as standard practice for treating patients with locally advanced disease [30, 31].

However, improved surgical techniques mean that radical resection is also a viable option, especially when there are concerns of extra-prostatic involvement [28]. Improvements in diagnostic imaging (i.e. MRI) aid preoperative planning with regard to the extent of surgical resection [33].

Locally advanced PCa typically disseminates in a predictable pattern to the surrounding tissues, including the bladder, lymph nodes, seminal vesicles and in rarer cases the rectum [28]. Pelvic exenteration, when indicated, aims to achieve complete tumor clearance, while ensuring an acceptable QoL. The complexity of the procedure means surgeons must be familiar with a variety of techniques including reconstructive options. As a result, many advocate the centralization of exenterative procedures in high-volume centers, as these have produced improved survival outcomes with acceptable morbidity rates (table 2) [23].

To date the largest reported series of exenterative surgery was by Zincke et al. [34] in 1992. This compared pelvic exenteration versus radical prostatectomy for the management of locally advanced PCa following radiotherapy. There was no observed improved survival benefit in either group, although the exenterative group did suffer higher rates of postoperative complications.

However, there is evidence to support the role of pelvic exenteration in select cases of advanced PCa. Bulky disease (locally advanced or recurrent) can cause significant symptoms including genitourinary/gastrointestinal bleeding or obstruction; therefore, pelvic exenteration may be indicated [35]. Rarely, it is the surgical modality of choice in the presence of synchronous prostate and rectal cancer [36], or as a viable and important treatment option for patients suffering severe pelvic pain as a sequelae of advanced disease that is not amenable to medical therapy [37].

The role of radical surgery in locally advanced PCa, node positive PCa and even oligometastatic PCa is becoming increasingly recognized with patients that have a good performance status [38].

Role of Palliative Exenteration

Both locally advanced bladder and prostate cancer can present with substantial complications including bleeding, pain, dysuria and urinary obstruction [39]. Chronic obstruction of the ureters and/or bladder can result in renal impairment/failure with some patients requiring indwelling long-term urinary catheters/stents or nephrostomy tubes. In addition, severe pelvic pain due to local invasion into the sacrum or rectum can quickly prove refractory to medical management [40].

Initially palliative radiotherapy (with/without hormonal therapy) should be offered to those with advanced unresectable bladder or prostate cancer [19, 41]. In addition, the input of a pain specialist is vital to help control analgesia needs, especially when dealing with perineal pain. When the above options have been exhausted, selective palliative exenteration may be considered for symptom relief [27]. Kamat et al. [42] observed an overall improvement in pain symptoms, with 78% of patients having complete resolution of intractable pelvic pain. Cystoprostatectomy provides a durable response to patients with symptomatic bladder invasion from PCa [43]. However, exenteration is associated with considerable morbidity and therefore careful patient selection is paramount to success. The primary goal of palliative surgery is to improve QoL, while minimizing the extent of surgical resection [44]. However, not all patients are suitable candidates for palliative exenteration [44, 45]. In addition, patients must be well counselled before resection, with good radiological assessment performed to ensure that progression of disease or death is not likely to outpace recovery time [46]. Ultimately, the patient must also be able to manage fecal or urinary diversion.

Urinary Diversion

The first urinary diversion techniques were described in 1852 [47]. Options for urinary diversion following radical cystectomy can be divided into continent and in-
continent diversions. Currently, orthotopic neobladder and ileal conduit represent the vast majority of urinary diversions performed [48].

To date, there is considerable debate as to which urinary diversion should be utilized with a lack of significant evidence favoring one particular technique [19]. There are several factors that can influence the choice of diversion post cystectomy. The neobladder is a technically more challenging surgical procedure; however, it avoids the need for a stoma and the associated complications and psychosocial downsides. Patient factors play an important role in the selection of the urinary diversion, especially in the case of the neobladder. A patient’s co-morbidities must also be fully assessed and the selected diversion should provide good functional and oncological outcomes and an acceptable postoperative QoL.

### Ileal Conduit

To date, this remains the most popular urinary diversion techniques over the last 30 years [49]. The procedure consists of harvesting a section of ileum approximately 12–18 cm in length. Care must be taken to preserve an adequate length of terminal ileum in order to prevent metabolic disturbances secondary to issues with salt absorption. Ureters are Anastomosed to the harvested ileal conduit, with the distal portion exteriorized through the abdominal wall, typically in right abdominal quadrant and covered by a stoma bag [50]. Key proponents of this technique cite low complication rate, with the main issues occurring early due to the anastomosis [51].

### Orthotopic Neo bladder

The orthotopic neo bladder has been popularized by Studer [52]. This procedure involves using a segment of colon or ileum that is detubularized and formed into a reservoir. This creates a reservoir able to hold approximately 400–500 ml in a relatively low-pressure system. The neobladder is then joined to the patient’s urethra, allowing the patient to naturally void with the aid of a Valsalva maneuver [53]. Contemporary data from large volume series observed that orthotopic substitution is now utilized in approximately 80% of men and up to 50% in women [48]. Main contraindications to orthotopic diversion include tumor infiltration into the bladder neck or urethra, impaired kidney function, inflammatory diseases of the intestine, or complex urethral stricture disease [54]. Furthermore a well-motivated patient is of paramount importance due to the strict bladder emptying regime, with patients required to perform regular daytime and nocturnal voiding to prevent rupture in the postoperative period as well being able to perform intermittent self-catheterization when the need arises [49].

### Cutaneous Ureterostomy and Rectosigmoid Diversion

These are older techniques of incontinent urinary diversion, which have generally fallen out of favor. The cutaneous ureterostomy involves detaching the ureters from the bladder and diverting them to the abdominal wall. It suffers from complications such as ureteric stenosis and ascending urinary tract infections (UTIs) [55]. Rectosigmoid diversion is the oldest technique of urinary diversion, which involves attaching the ureters to the rectosigmoid colon. This utilizes the competent anal sphincter to form a continent urinary diversion. However, this procedure is very uncommon due to concerns regarding developing colon cancer and the high incidence of UTI/pyelonephritis [56].

### Complications Associated with Pelvic Exenteration

Pelvic exenterative surgery is extremely challenging and is associated with considerable morbidity and mortality, with initial perioperative mortality rates of > 20% [2]. However, modification of surgical techniques combined with improved perioperative care reduced associated morbidity and mortality. This was due largely to improved surgical technology, management of intraoperative blood loss, and better anesthesia and critical care [57]. In addition, improvement in reconstruction options (urinary diversion and advancement flaps) has resulted in an increased number of patients willing to undergo the procedure in recent decades.

Traditionally, the majority of pelvic exenterations were not performed in specialist high volume centers, with multidisciplinary teams input [10]. Screening programmes result in earlier detection, with the median age of patients having exenteration being younger [45]. Modern series on pelvic exenterative surgery have demonstrated a 30-day mortality rate of less than 2%. Morbidity rates remain variable, ranging 13–64%, with at least 1/3 having a major complication [18]. Major complications following pelvic exenterative surgery for urological malignancies are primarily related to issues with urinary diversion, but obstruction, anastomotic issues and fistulas have been widely documented [58]. Approximately 1/5 of patients will require an additional procedure/surgery to deal with a complication [59]. Common minor complications typically include wound issues/surgical site in-
Infections, postoperative lower respiratory tract infection, blood transfusion and/or UTI.

QoL Assessment

The QoL data pertaining to exenterative surgery are following resection for colorectal or gynecological malignancies [60, 61]. To date, there are sparse reports on QoL impact following exenteration for urological neoplasm. A recent systematic review by Cerruto et al. [62] observed a statistical difference in QoL in favor of patients undergoing ileal orthotopic neobladder versus ileal conduit. Singh et al. [63] also demonstrated superior QoL outcomes (physical function, social function and global health) in patients undergoing orthotopic neobladder reconstruction compared to ileal conduit. It has also been noted that improved health-related QoL outcomes are independent prognostic factors in overall survival [64].

Accurately measuring the impact of exenteration on QoL is a challenge due to the variety of domains affected by the procedure. There is a multifaceted effect to physical and sexual function, body and social image issues and psychological health [65]. In addition, there is significant heterogeneity in surgical techniques and methods regarding the reporting of outcomes (table 3) [66].

There is also lack of standardized formal assessment tools and prospective data, with the majority of data coming from small retrospective series. Current assessment tools include the SF-36v2, which assesses the impact of disease on general and specific cohorts [67]. Alternatively, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a 30-question module that generic reviews QoL in patients with cancer [68]. More specific scoring systems for invasive BCa include the QLQ-BLM30 score [62]. Early health-related QoL tools for patients with PCa such as the EORTC prostate module-QLM-P14 [69] or Prostate Cancer-Specific Quality of Life Instrument [70] were designed for patients with advanced disease. The EORTC QLQ-PR25 has been validated for use in patients with varying disease stage and with different treatment modalities [71]. Prospective collaborative groups aim to standardize the assessment of QoL impact following exenterative surgery. In addition, patient reported outcomes reporting will also help aid both surgeons and patients in planning and decision making prior to embarking on exenterative surgery.

Future Developments and Expansions

Open radical cystectomy with/without exenteration remains the gold standard treatment for MIBC. New minimally invasive techniques (laparoscopic and robot-assisted surgery) are being examined and promoted.

Laparoscopic Exenteration

This places significant demands on the patient and the surgeon alike, due to prolonged operative times, requiring highly developed laparoscopic skills, including intra-corporeal suturing. Puppo et al. [72] described APE in 5 females through a combined transvaginal and laparoscopic approach in 1995. It was soon shown that the entire procedure could be completed intra-corporeally with an ileal conduit formation [73]. A recent review by Tang et al. [74] concluded that laparoscopic exenteration is safe and feasible to open surgery; however there is a lack of large-scale data or long-term follow-up.
Robotic Exenterative Surgery

The da Vinci system that was introduced in 2001 prompted many to utilize it for complex pelvic and exenterative surgery [75]. Proponents cited the easier learning curve, better optics, reduced technical difficulties including fatigue, surgeon ergonomics, tremor, and better intra-corporeal suturing [76]. A study from Memorial Sloan Kettering compared open radical cystectomy (n = 58) with robotic-assisted radical cystectomy (RARC) and open diversion (n = 60). The RARC group had less blood loss but longer operative time and higher cost. Length of hospital stay, QoL and pathological results were similar. The study was limited by lack of long-term outcomes [77]. However, Yuh et al. [78] in their systematic review noted similar oncological outcomes at 5-year follow-up in RARC groups but concluded that more prospective data is needed.

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