Surgical Advances in Bladder Cancer
At What Cost?

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KEYWORDS

• Bladder cancer • Alvimopan • Blue-light cystoscopy • Robotic cystectomy • Costs • Quality of life

KEY POINTS

- Bladder cancer is one of the most expensive cancers to treat; however, funding for research, discovery, and innovation is relatively lacking.
- Blue-light cystoscopy is a novel diagnostic and therapeutic technique that improves detection of superficial bladder cancer and reduces costs associated with tumor recurrence.
- Alvimopan, an oral opioid receptor antagonist, reduces the incidence and costs of complications associated with postoperative ileus after radical cystectomy and small bowel urinary diversion.
- Robot-assisted radical cystectomy is an oncologically acceptable alternative to open cystectomy; however, further investigation is necessary to determine the cost-effectiveness of this technology.

INTRODUCTION

From diagnosis to death, bladder cancer is the most expensive malignancy to treat in the United States, with estimated expenditures of up to $187,000 per incident case.[1,2] Bladder cancer treatment accounted for approximately $4 billion in direct costs to the US health care system in 2010 and is expected to exceed $5 billion by 2020.[3]

Direct costs related to the management of non-muscle invasive bladder cancer (NMIBC) are driven by regular surveillance cystoscopies, frequent cross-sectional imaging and repetitive transurethral resections of bladder tumors (TURBT), and intravesical therapies.[4–6] Patients typically have prolonged survival with frequent recurrences resulting in the high lifetime cost of this disease. Given that approximately 75% of incident cases are in this subgroup, the potential economic and public health impact of innovation in NMIBC is substantial.

For patients with muscle-invasive bladder cancer (MIBC), the standard of care is radical cystectomy (RC) with bilateral pelvic lymph node dissection and urinary diversion.[4–6] Despite improvements in surgical techniques and postoperative recovery pathways, this complex and challenging procedure remains highly morbid with up to 60% of patients experiencing a complication[7–9] and 25% requiring readmission to the hospital within 30 days.[10] In addition to the high cost of surgery and management of subsequent complications, perioperative chemotherapy, and frequent cross-sectional surveillance imaging, as well as high end-of-life costs, contribute to the substantial financial burden of advanced disease.[11] In addition to the direct medical costs associated with health services expenditures, the societal value of life lost because of untimely death from bladder cancer in the year 2000 alone is estimated to be as high as $17 billion.[12]

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Surgical advancements and novel diagnostic and therapeutic techniques are essential to improve bladder cancer outcomes and reduce the burden of suffering. However, the cost-effectiveness of these advances has never been more relevant as pressure mounts on the health care system to contain costs. Bladder cancer represents an enormous opportunity to maximize the value of treatment to improve outcomes while reducing excessive expenditures.[13] This article examines the effectiveness and costs associated with recent advances in the surgical management of bladder cancer. In the first section, the evidence regarding blue light cystoscopy as an innovation in NMIBC is discussed; subsequently, with regard to patient care for higher risk disease, the novel perioperative pharmaceutical, alvimopam, and robotic-assisted radical cystectomy (RARC) are evaluated.

BLUE-LIGHT CYSTOSCOPY

Rationale

Complete TURBT is paramount to optimizing oncologic outcomes and minimizing costs.[14] Approximately 60% of patients with newly diagnosed NMIBC have an "early recurrence" within 1 year after initial TURBT.[15] Because nearly one-third of patients undergoing repeat TURBT within 6 weeks of initial resection have residual tumor, a substantial proportion of these recurrences may represent incomplete initial resection.[16] Although solitary, pedunculated, papillary lesions are adequately visualized and resected with traditional white-light cystoscopy (WLC), the risk of incomplete detection and/or tumor resection with WLC is particularly high with flat, sessile, multifocal lesions characteristic of carcinoma in situ (CIS).[17–19] Intravesical therapies are intended to treat and prevent implantation of microscopic tumor cells rather than gross residual tumor burden. Recurrence, progression, and overall prognosis are therefore strongly predicated on the completeness of the initial TURBT.

Description

Blue-light cystoscopy (BLC) or fluorescence cystoscopy was developed to improve detection to increase the likelihood of complete TURBT. This optical-imaging technology uses a photosensitizing agent in combination with blue-light illumination (380–450 nm) to help differentiate between malignant and benign urothelium. The photosensitizing agent is actively transported into urothelial cytoplasm and incorporated by the cellular heme-biosynthesis metabolism. The photoactive component (photoporphyrin IV) accumulates in cancerous and precancerous cells as a result of abnormal enzyme activity, while normal tissue eliminates the photoactive substance. When illuminated by blue light, abnormal cells fluoresce red from the accumulation of photoporphyrins and are more easily differentiated from the bluish-green appearance of normal cells.[20]

The original photosensitizing agent, 5-amnolevulinic acid (5-ALA), required a 2- to 4-hour intravesical dwell time before TURBT and is no longer commercially available. Hexaminolevulinate (HAL; Cysview, PhotoCure Inc, Princeton, NJ, USA; formerly Hexvix, Photocure ASA, Oslo, Norway) is a derivative of 5-ALA that was approved for use in Europe in 2006 and in the United States in 2010.[21] HAL and 5-ALA are equally effective[22]; however, HAL is more stable in white light, has better fluorescent intensity, has more homogeneous enhancement and distribution within photoactive porphyrins, and requires only 1 hour of dwell time.[23]

Efficacy

Literature summary

Two meta-analyses by were published in 2013 by Yuan and colleagues[24] (12 articles from 11 studies, 2258 patients, 1114 receiving BLC, including patients receiving 5-ALA and HAL) and Burger and colleagues[18] (10 articles from 9 studies, 2212 patients, 1345 receiving BLC, only HAL). The meta-analysis by Burger and colleagues used raw patient-level data from prospective studies of patients receiving only HAL and provides the strongest level of evidence for the benefit of BLC. Rink and colleagues[25] also published a systematic review of 44 studies comparing both 5-ALA and HAL with WLC in 2013.

Increased detection

Ta/T1 Burger and colleagues[18] demonstrated significant improvement in the detection of papillary lesions with BLC using HAL (95% vs 86%, odds ratio [OR] 4.9 $P<.0001$). The odds of detecting a T1 lesion were 2.3 times higher with BLC than with WLC. One in 4 patients had at least 1 additional tumor detected by BLC that was missed with WLC in this meta-analysis. This proportion of patients with a missed tumor on WLC detected by BLC was significant in both primary (20.7%) and recurrent (27.7%) disease as well as intermediate-risk (35.7%) and high-risk (27.0%) disease. The detection rate in studies reviewed by Rink and colleagues[25] using BLC was 92% to 100% compared with 50% to 100% using WLC.

Carcinoma in situ The odds of detecting CIS was 12.4 times higher with BLC than WLC (95% vs 59%, $P<.0001$) with 26.7% of patients having

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