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TOPIC PAPER

Economic aspects of bladder cancer: what are the benefits and costs?

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Abstract
Objective Bladder cancer (BC) has the highest lifetime treatment costs per patient of all cancers. The high recurrence rate and ongoing invasive monitoring requirement are the key contributors to the economic and human toll of this disease. The purpose of this paper was to utilize the recent literature to identify opportunities for improving the benefits and costs of BC care.
Methods A PubMed search was performed of recent publications concerning (BC) cost-effectiveness. We reviewed studies, reviews, opinion papers and cost-effectiveness analyses, focusing primarily on non-muscle-invasive bladder cancer (Ta/T1; NMIBC).
Results New diagnostic tools such as urine markers may assist in more cost-effectively detecting BC at an earlier stage, however, these markers cannot replace the cystoscopy, which is the current standard of care. A photodynamic diagnostic tool (PDD) using hexylaminolevulinate (Hexvix®) enhances tumor visibility and improves transurethral resection of bladder cancer (TURB) results, potentially reducing recurrence rates and lowering treatment costs. While the importance of BC research has been acknowledged, research investment has been continuously reduced during the last 5 years.
Conclusions The economic burden of BC is well-characterized in the literature. This study suggests that new technologies (i.e., urine-based tests, PDD) and therapeutic regimes (intravesical chemotherapy, adjuvant immunotherapy) have significant potential to improve the diagnosis, treatment and on-going monitoring of BC patients, with potential improvements in clinical outcomes and concurrent cost-savings. A renewed interest and investment in BC research are required to ensure future advancements.

Keywords Bladder cancer · Diagnosis and treatment · Fluorescence cystoscopy · Imaging technology · Economic and cost considerations · Intravesical chemotherapy · TURB · PDD · NIMBC · Hexvix

Background and objective

Bladder cancer (BC) has the highest lifetime treatment costs per patient (pp) of all cancers, followed by colorectal, breast, prostate, and lung cancer [1]; costs have increased steadily since 1996 [2]. Worldwide, 336,000 patients were diagnosed with BC in 2000 [2]. The American Cancer Society estimated 50,040 incident cases for 2007 [3], and treatment costs for non-muscle invasive bladder cancer (NMIBC) in the United States (US) are estimated at $157.5 M over 5 years [4]. Although most patients present with NMIBC (70% (78% females; 64% males)), the high rate of recurrence and disease progression necessitates vigilant long-term monitoring for BC patients.

The enormous human, psychological and economic burden of BC underscores the importance of optimizing diagnosis and treatment protocols. However, relevant data are sparse, making it difficult to adequately assess cost benefit for current standards of BC care. The purpose of this paper was to use the available BC data to identify potential opportunities for improving the overall cost benefit profile of BC care.

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Methods

A PubMed search was performed on literature published between 2003 and 2008 using MeSH terms: cost-effectiveness, screening, tumor markers, photodynamic diagnostic (PDD), transurethral resection of the bladder (TURB) and BC. The search included prospective and retrospective studies, reviews, opinion papers, and cost effective analyses as well as European Association of Urology (EAU) and American Urology Association (AUA) guidelines for NMIBC and muscle invasive BC (MIBC).

Results

Economic burden of bladder cancer

Depending on the country, BC costs from diagnosis-to-death range between $89,287 and $202,203 pp [5] and will likely increase as survival rates increase. In the US, 2006 total cancer costs were estimated at $206.3B with estimated productivity losses of $17.9B for cancer-related morbidity and $110.2B for cancer-related mortality [3]. On average, 12 years of income-producing life are lost with each premature death [6]. Among cancers in the US, BC has the highest pp treatment costs, and the 5th highest overall cost [5], estimated at $3.4B annually with $2.9B in direct treatment-related costs, and indirect costs of $184,762 to $461,907 pp [7].

The United Kingdom (UK) reported a 2001–2002 total NMIBC and MIBC costs of £55.39 M ($82,395 M) or £8,349 pp ($12,409), of which 60% was spent managing NMIBC [8]. This cost differential likely stems from the higher incidence, recurrence, and survival rates of NMIBC [8]. NMIBC has an average 60–80% recurrence rate, of which 40–60% recurs within 2 years, with 10–30% of the patients progressing to MIBC which requires more invasive and costly treatment [9]. Monitoring, which is essential given the high BC recurrence rates, generates significant on-going costs. About 75% of the post-diagnosis costs relate to pre-operative and intra-operative management including post-surgical complications, tri-annual examinations and semi-annual diagnostic and laboratory testing [10].

Several strategies for reducing BC's economic burden have been proposed: (1) use of urine-based markers to identify incident or recurrent tumors earlier [8]; (2) use of outpatient facilities for TURB reducing hospitalizations if surgical risks can be minimized [8]; (3) improve efficacy of intravesical treatments. Finally, but not yet proven, is the use of photodynamic diagnosis (PDD), instead of conventional white-light cystoscopy, to improve initial TURB efficacy and potentially reduce NIMBC's residual risk [11].

Potential role for non-invasive diagnostic tools

With an estimated 4% incidence in a healthy population, BC screening results in a 3.0 life-year gain per 1,000 patients, a 50% reduction in disease progression and a cost savings of $101,000 pp [12]. Although urine-based markers, like NMP-22, seem to be cost-effective for the high-risk population, they will not reduce cystoscopy requirements and must be tested in prospective trials to determine their value in the general population. The estimated cost per diagnosis (i.e., direct cost divided by observed sensitivity) for NMP-22 is ($39.82), cytology ($54.96), cystoscopy ($430.14), and CT urogram ($989.06). Cystoscopy was more sensitive than the other modalities in diagnosing BC ($P < 0.05$), although the combination of cystoscopy with other tests yielded no statistically significant improvements in sensitivity [13].

Potential to improve clinical outcomes and cost of care

After hematuria, positive cytology or positive urine-based markers, a diagnostic cystoscopy is performed, followed by TURB if needed. The average annualized rate of TURB in US Medicare patients with a BC diagnosis is 51% and is generally consistent across genders, geographic regions, and racial and ethnic groups. The annualized TURB rate varies by age, ranging from 46% among 65–69-year-olds to 60% among 90–94 year old beneficiaries [14].

TURB represents, by far, the largest BC expenditure, accounting for 71% of treatment costs in the UK [8]. Table 1 shows TURB costs in Europe, ranging from €845 ($1,124) (France) to €2,231 ($2,967) (Germany) [15]. Costs are similar in Japan (¥281,600 ($2,428)) but higher in the US $5,305 (€3,453) [16].

The quality and result of the initial TURB strongly determines the patient's prognosis and overall BC treatment costs.

Table 1 Average European BC treatment reimbursement (procedure and hospital stay inclusive)

	UK in £ ($)	Germany in € ($)	France in € ($)	Italy in € ($)	Belgium in € ($)
Cystoscopy	**422 (620)**	46 (61)	**38 (51)**	57 (76)	40 (53)
TURB	1,465 (2,154)	**2,231 (2,967)**	**845 (1,124)**	2,061 (2,741)	1,655 (2,201)
Cystectomy	**3,867 (5,684)**	**15,419 (20,507)**	9,697 (12,897)	7,222 (9,605)	10,932 (14,540)

The bolded amounts highlight the lowest and highest reimbursement

$ The exchange rate was calculated on the basis of 1Euro = 1.33 US$ and 1£ = 1.47US$

Table 2 TURB cost calculation: comparison of conventional TURB versus PDD assisted TURB based on a diagnose related group in a German Hospital

Cost parameter	Conventional TURB in € ($)	PDD assisted TURB in € ($)	Difference in (±) € ($)
Preop.catheter	0,00 (0,00)	23,00 (30,59)	+23,00 (+30,59)
Hexvix®	0,00 (0,00)	412,50 (548,62)	+412,50 (+548,62)
Equipment/10 years[a]	7,10 (9,44)	10,70 (14,23)	+3,60 (+4,78)
Bladder TURB[b]	900,00 (1197,00)	900,00 (1197,00)	0,00 (0,00)
Histology tumor	40,63 (54,03)	40,63 (54,03)	0,00 (0,00)
Histo 4 corner Bx[c]	121,38 (161,44)	0,00 (0,00)	−121,38 (−161,44)
20% chance of 2nd TURB after 3/6 mos. (DRG)[d]	458,00 (609,14)	0,00 (0,00)	−458,00 (−609,14)
Total/TURB	**1527,11 (2031,06)**	**1386,83 (1844,48)**	**−140,28 (−168,57)**

DRG Diagnosis related group

[a] Hardware equipment cost calculated for an individual TURB and PDD based on an estimated 300 TURBs/year over 10 years

[b] TURB cost (includes average time of surgeon, anethesiologist, nurse/technician, equipment cost)

[c] Pathologist cost for four random biopsies

[d] The chance of a re-TURB in relation to the published results of D'Hallewin et al. [40] and Daniltchenko et al. [18]

Source University of Tuebingen, Department of Urology

$ The exchange rate was calculated on the basis 1Euro = 1.33 US$

Photodynamic diagnosis

Photodynamic diagnosis (PDD) is an emerging technology with significant potential for improving the effectiveness of TURB. PDD was introduced using 5-aminolevulinic acid (5-ALA). Since 2005, hexylaminolevulinate (HAL or HEXVIX®) has been approved in 27 European countries and recommended in EAU NIMBC Guidelines [17–20]. Hexylaminolevulinate induces protoporphyrin IX (PpIX) production in the bladder where the increased PpIX build-up better illustrates precancerous and cancerous lesions. When performing a PDD blue light cystoscopy, PpIX fluorescence is produced by excitation with blue light resulting in a red-to-purple fluorescence.

PDD supports a more complete resection [11] and has been reported as improving oncological patient outcome, reducing recurrence rates by approximately 20 and prolonging recurrence-free survival [21]. The learning curve for PDD TURB resulting in a more complete tumor resection can be shortended by utilizing the virtual TURB training system (Karl Storz® Tuttlingen, Germany) [22].

The experience of the author's department (Table 2) illustrates Daniltchenko et al.'s hypothesis that the initial PDD costs can be offset by fewer TURB follow-ups [18]. In a separate prospective series of 115 patients (void of adjuvant treatment), recurrence rates after 60 months were 59% after PDD and 75% following white-light cystoscopy. The researchers in that study estimated that, in using PDD, they have avoided at least 20 additional TURBs over a 5-year follow-up, clearly demonstrating that the benefits associated with PDD outweigh the costs [23].

The statistically significant advantage of decreased BC recurrence after PDD has been reported to persist for at least 8 years [21]. Hedelin et al. concluded that if PDD were used in high-risk patients (15% of all newly diagnosed BC patients estimated at 1720 new cases of BC per year in Sweden alone), it could save €500 K ($665 K) in the first year alone. If PDD were used for all TURBs in high and medium risk patients, the first year savings would be €405,000 ($536,650) and €363,000 ($482,790), respectively [24]. A recent German study also revealed that PDD significantly reduced costs related to recurring NMIBC [19].

Intravesical chemotherapy and adjuvant immunotherapy

Depending on tumor stage, the EAU guidelines recommend intravesical chemotherapy or adjuvant immunotherapy following TURB. Two primary drugs are currently used: alkylating agents like mitomycin (MMC) and different strains of Bacillus Calmette-Guerin (BCG) [17].

MMC is generally considered the first-line agent for low-risk tumors and can be administered immediately after TURB, however, this practice is considered "*unlabelled*" in the US and some other countries [5]. In patients with intermediate and high-risk BC tumors, a single administered shot of intravesical chemotherapy should be followed by additional instillations or BCG [17]. MMC after TURB has reduced recurrence by as much as 50% compared with transurethral resection alone [25].

Tolley et al. [26] reported a statistically significant decrease in the tumor recurrence in NMIBC patients treated

with MMC within a 24-h period following TURB compared to those who did not receive instillation. If the instillation was performed the following day, the relative risk of tumor recurrence was estimated to be doubled [27]. Bohle et al. [28] conducted a meta-analysis comparing 1328 NMIBC patients treated with adjuvant-MMC versus 1421 patients treated with BCG. Without a clear separation between intermediate and high-risk patients, the overall recurrence rate was 46.4% for MMC and 38.6% for BCG after a 26-month mean follow-up. MMC demonstrated fewer side effects. Comparable beneficial effects have been demonstrated for MMC, epirubicin, and doxorubicin [25]. BCG is generally reserved for high-risk tumors and first-line treatment for carcinoma in situ [29]. If the risk of an adverse reaction prevents the use of BCG for carcinoma in situ, intravesical MMC may be given instead [30]. Uchida et al. [16] reported the mean total BCG treatment cost was ¥224,566 ($1,936)pp. Their 5-year recurrence-free patient survival rate with and without BCG instillation therapy was 78 and 28%, respectively. Accordingly, the cost-effectiveness ratio was ¥449,132 ($3,872) over 5-year recurrence-free period (60,906 ¥/year;$525/year) [16].

Kilbridge et al. [31] found that an average 65-year-old male with high-grade superficial disease treated with BCG gains 6 months life expectancy at an incremental cost of $1,660, or $3,320 per year of life saved. The incremental cost effectiveness of BCG was still better than many other accepted medical practices. Both BCG and MMC are considered superior to other intravesical agents (such as interferon-α or anthracycline antibiotic-related chemotherapy) for reducing recurrences; however, it is unclear if any intravesical therapy ultimately affects the rate of progression to MIBC [32].

Bottemann et al. [5] estimated the cost-benefit ratio in 100 new NMIBC patients treated with adjuvant intravesical chemotherapy; 20 would be tumor-free at 3 months and would no longer require further TURBs resulting in savings of £30,000 ($44,100). It could be expected that a lower recurrence risk would lead to a less intensive cystoscopic follow-up regime, resulting in further potential savings in the first year post-initial TURB of approximately £13,500 ($19,845) (HRG estimate of cystoscopy cost £450 ($662) resulting in 30 less cystoscopies annually). This example suggests a net savings of £45,500 ($66,882) per 100 new NMIBC patients.

The combination of PDD TURB and MMC intravesical instillation might help to reduce the BC recurrence that would help to reduce the cost over the long term.

Cost consequences of disease progression

The MIBC patient treatment costs are nearly three times those for patients with stage Tis/Ta and two times for those patients with TNM stage T1. On average, the bladder-related complications contributed $249, $384, and $775 to the monthly patient costs with stage Tis/Ta, T1, and MIBC, respectively. Systemic-related complications (SRCs) added monthly costs averaging $500 in 21% of the patients with NMIBC and $700 in 40% of MIBC patients. The mean, annual post-diagnosis continuing care costs pp were estimated at $4,975, $7,100 and $17,437 for those with Tis/Ta, T1 and MIBC [33]. The US Medicare annual cost for continuing care for the 3634 NMIBC patients and 2083 with MIBC totaled $21 million and nearly $36 million, respectively. During the preceding 4 months, BC-related care added an estimated $4.7 million to each total [33].

Konety et al. reported median total charges of $53,342 for patients with radical cystectomies. Medical complications, which occurred in approximately 28% of patients increased costs at least $15,000 [34]. The total annual incremental medicare expenditures for MIBC patients, with and without adjustment for co-morbidity, were more than twice those of NMIBC patients (2006 US $99.3 M versus $41.8 M, respectively) [33].

Avritscher et al. [35] estimated the BC lifetime mean treatment cost at $99,270 for MIBC patients and $120,684 for NMIBC patients, with an annual average of 36 hospitalization days for MIBC patients vs. 1.3 days per year for NMIBC patients. Admissions and surgical procedures accounted for 50% of the total costs ($32,559) and surveillance for and treatment of tumor recurrences, accounted for 60% ($39,393). In addition, 30% of the total cost ($19,811) was attributable to treatment of complications: 26% ($16,934) for MIBC and 4% ($2,312) for NMIBC.

Progression from NMIBC to MIBC clearly increases overall treatment costs. Early detection of incident and recurrent disease plays a key role in reducing the risk of disease progression, as do emerging technologies, such as PDD, and adjuvant therapies, such as MCC and BCG.

Economic impact of cancer on patients and families

There is another side of the enormous financial burden that cancer exerts on patients and their families. Low-income patients undergoing cancer treatment spent approximately 27% of their annual income on out-of-pocket medical expenses [36]. Twenty-seven percent had to delay or forego treatment and 6% filed for bankruptcy [37]. A study by Yabroff et al. [38] showed that the estimated patient's cost for time spent traveling, waiting for appointments and receiving services or procedures during the first 12 months after diagnosis was as much as $5605.

Bladder cancer research investment

Sangar et al. [8] commented that research funding allocation in the UK for BC is not commensurate with its financial

burden. They estimate that BC and prostate cancer incur similar annual healthcare costs pp yet research funding varied markedly, with £4.62 M ($6.808 M) for BC and £20.56 M ($30.295 M) for prostate cancer. In the US, the NCI's investment [39] in BC research decreased from $35.5 M in fiscal year 2003 to $19.8 M in fiscal year 2007 for one of the highest ranked cancers; conversely, total cancer research investment increased $4.6 to $4.8B [39].

Conclusion

Current state-of-the-art NMIBC and MIBC treatments incorporate recently developed diagnostic and therapeutic tools like urine-based markers or HAL-photo dynamic diagnostics that further increase the initial BC treatment cost. More cost-effective treatments are essential in BC therapy, especially in this current financially-strained time. This topic paper concludes that, while these new treatment options initially provoke higher costs after the initial diagnosis, long-term cost benefits can be achieved through reduced tumor recurrence and potentially reduced progression rates.

In addition to PDD use, the training of urologic surgeons must be improved as the chosen initial surgical therapy has a profound impact on the patient and total BC costs. Special attention should be considered in future studies with the combined use of HAL-PDD, intravesical MMC chemotherapy and other treatment possibilities where diagnostic and treatment tools will not only be evaluated with the clinical sensitivity and specificity in mind, but also judged by their long-term cost effectiveness. A renewed interest and investment in BC research are essential to ensure future advancements.

Conflict of interest statement There is no conflict of interest.

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