Published in final edited form as:

Cancer. 2009 June 15; 115(12): 2660–2670. doi:10.1002/cncr.24311.

Treatment of Non-Muscle Invading Bladder Cancer: Do physicians in the United States Practice Evidence Based Medicine? : The use and economic implications of Intravesical Chemotherapy after Transurethral Resection of Bladder Tumors

Ralph Madeb¹, Dragan Golijanin¹, Katia Noyes², Susan Fisher², Judith J. Stephenson³, Stacey R. Long³, Joy Knopf¹, Gary H. Lyman⁴, and Edward M. Messing¹

¹ Department of Urology, University of Rochester School of Medicine, Rochester, New York

² Department of Community and Preventive Medicine, University of Rochester School of Medicine, Rochester, New York

⁴ Department of Medicine, University of Rochester School of Medicine, Rochester, New York

³ Department of Outcomes Research, MEDSTAT, Inc., Philadelphia, Pennsylvania and Ann Arbor, MI, USA

Abstract

Background—Phase III clinical trials performed primarily outside the United States (U.S.) demonstrate that intravesical instillation of chemotherapy immediately following transurethral resection of a bladder tumor (TURB) decreases recurrence rates. We sought to determine whether U.S. urologists have adopted this practice, and its potential effect on costs of bladder cancer (BC) care.

Methods—Using 1997–2004 MEDSTAT claims data, we identified patients with newly diagnosed BC who underwent cystoscopic biopsy or TURB, and those who received intravesical chemotherapy within one day after TURB. Economic consequences of this treatment compared to TURB alone were modeled using published efficacy estimates and Medicare reimbursements. We used a time horizon of 3-years and assumed that this treatment was given for all newly diagnosed low risk BC patients.

Results—Between 1997 and 2004, we identified 16,748 patients with newly diagnosed BC, of whom 14,677 underwent cystoscopic biopsy or TURB. Of these, only 49 (0.33%) received same day intravesical instillation of chemotherapy. From 1997 through 2004, there has been little change in the use of this treatment. We estimated a 3-year savings of \$538 to \$690 (10 to 12%) per patient treated with TURB and immediate intravesical chemotherapy compared with TURB alone, reflecting a yearly national savings of \$ 19.8 to \$24.8 million.

Conclusion—Instillation of intravesical chemotherapy immediately after TURB has not been embraced in the U.S. Adopting this policy would significantly lower the cost of BC care.

Keywords

Intravesical therapy; Bladder Cancer; Evidence Based Medicine; Transurethral resection of bladder tumor

INTRODUCTION

Bladder cancer is the fourth most commonly diagnosed cancer in men and the eighth in women in the United States (U.S.). An estimated 61,420 new cases will be diagnosed in 2007 and 13,060 patients will die of this disease(1).

Seventy-five percent of newly diagnosed bladder cancers are non-muscle invasive (NMI) (2;3). These cancers often recur after seemingly complete transurethral resection (TURB) because of new tumor development in other regions of the urothelium, tumor cell implantation resulting from spontaneous perturbations or those induced by instrumentation, and/or incomplete resection of the original malignancy. (4;5)

While recurring well and moderately differentiated NMI bladder cancer rarely progresses to a life-threatening condition, repeated TURBs and courses of intravesical instillations of immuno- and chemotherapeutic agents cause considerable inconvenience, expense, and morbidity. A single instillation of chemotherapy immediately after TURB has been proposed as a means of reducing recurrence by decreasing procedure facilitated tumor implantation and eradicating field effect or persistent (incompletely resected or unrecognized) tumors(5–7). For over a decade, several prospective randomized-controlled clinical trials have shown that this treatment is safe and decreases recurrences by 17–44% compared with controls11–13 (Table 1), particularly for patients with newly diagnosed bladder cancers(5–10). Agents used include mitomycin C, doxorubicin, thiotepa (all available in the U.S.), as well as epirubicin and epodil (neither available in the U.S.).

In view of this evidence, we set out to determine whether U.S. urologists have adopted this practice and to ascertain whether implementing post-TURB intravesical instillation therapy would be cost-saving.

METHODS

Data

The study was based on the analysis of individual medical claims provided by MEDSTAT (www.MEDSTAT.com), a healthcare information company currently following over 7 million covered lives, which provides benchmark databases and research services for managing costs and quality of healthcare in the U.S. We used MEDSTAT's Commercial Claims and Encounters (CCAE) and Medicare Supplemental Coverage claims databases which have been validated and used for oncological and non-oncological research studies. (11–13) These databases are generally representative of the U.S. population in terms of gender (49% male). The mean ages of the CCAE and Medicare populations were 34 and 74 years, respectively. This compares with a mean age of 72 for all Medicare beneficiaries and 75 if only those 65 years and older are included. A higher percentage of individuals included in MEDSTAT databases reside in the Southern U.S. (50%) than the general population, while 36% of Medicare beneficiaries live in the Southern U.S.. (14)

Study Sample and Drug Use

Using 1997–2004 MEDSTAT claims, we identified bladder cancer patients based on the International Classification of Diseases-9th Revision (ICD-9) code of 188.9. We chose 1997 because it was the first calendar year after a positive large randomized clinical trial using an agent readily available in the U.S. was reported in the American literature. (8;10;15) Several studies have examined the accuracy of ICD-9 coding for various conditions compared to medical records and physician assessment, and demonstrated significant sensitivity and specificity in identifying patients with index conditions (diabetes, chronic kidney disease, breast cancer, CVA, and stroke).(16–18) Figure 1 presents the algorithm used to identify

newly diagnosed patients with bladder cancer who received same-day post-TURB intravesical chemotherapy. We then identified patients who underwent cystoscopy with biopsy or TURB for any size bladder tumor (using Current Procedure Terminology [CPT] codes 52204, 52224, 52234, 52235, 52240). From these, using prescription drug claims and National Drug Code and CPT codes, we selected patients who received an intravesical instillation of a chemotherapeutic agent (mitomycin C, doxorubicin, or interferon alpha) on the day of, or the day following TURB. Administration of immediate intravesical therapy post TURB is billed as an outpatient/ambulatory procedure (CPT 51720) rather than a prescription drug since it can only be administered by qualified medical personnel. Use of administrative claims data for evaluation of patterns of health care use is quite common and has been validated(11–13). Moreover, since errors in billing would lead to problems with payments, the quality of billing data is generally high(19)

Cost and Utilization

Based on prospective, randomized studies reported in the English language literature, we identified standard care and likely outcomes for patients with newly diagnosed NMI bladder cancer after initial TURB with zero, one, two, or three episodes of recurrence over a 3 year period(20–29). To assign cost values to the typical utilization associated with each of the recurrence patterns, with and without immediate post TURB intravesical instillation of chemotherapeutic agents, we used Medicare reimbursement fees for the related procedures and medications (Table 2). We assumed that all predicted recurrences would be recognized at the first (3 month) cystoscopy after the most recent TURB. In one analysis we assumed intravesical Bacillus Calmette-Guerin (BCG) would be used after the initial recurrence, while in the second we assumed Mitomycin C would be.

The results for each analysis are presented as an average cost per patient for a three year period. For the group not receiving immediate post TURB instillation therapy, we assumed that 60% would not have a recurrence during this period.²⁶ For the first analysis, the initial recurrence would be treated with induction (and maintenance, if successful) BCG, and BCG + alpha interferon would be used after the second recurrence. For the group receiving same-day intravesical instillation therapy, we assumed that recurrences would be reduced by 25% and that initial and second recurrences would be treated with induction and maintenance BCG and BCG + alpha interferon, respectively, with the same the efficacy as for those not receiving same day intravesical instillation therapy who recurred.

In the second analysis, we assumed that six instillations of Mitomycin C would be given for the initial recurrence, and those experiencing a second recurrence would receive induction (and maintenance, if successful) BCG, while those with a second recurrence would receive BCG + alpha interferon. The efficacy of these agents was assumed to be the same as in our first analysis. The same assumption was made for the efficacy of immediate post TURB intravesical therapy as in the first analysis; a 25% reduction in first recurrences. The 3-year time horizon was chosen because the overwhelming majority of bladder cancer recurrences occur within this period (26). In addition, the the American Urological Association (AUA) protocol is set for intense follow-up for three years after the initial TURB to detect recurrence and then switches to a less intense regimen. Furthermore, we feel that the majority of patients do not undergo more than three resections of bladder cancer and therefore have spread it over a three year period which would typically seen in patients with low risk disease. We assumed that prior use of intravesical chemotherapy after TURB would have no effect on the progression of subsequently diagnosed muscle invasive bladder cancer. We did not apply discounting in this study since we did not anticipate a dramatic effect over a 3-year period.

Because same day intravesical instillation therapy is not recommended for high-grade or muscle invading cancers, TIS, or predominantly non-urothelial cancers, we assumed that no patients in our analysis had these cancers. To be very conservative in terms of predicting cost savings and effectiveness, we assumed no patient would progress to high grade, TIS, or stage T2+ disease during the period of follow-up (since progression to any of these stages/grades mandates more complex and expensive therapies).

Since there is wide variation in the reported efficacy of intravesical instillation therapy, we conducted a threshold analysis to estimate the minimal effectiveness of this treatment required to balance the added cost of medication and care compared to the standard TURB. To perform the threshold analysis, we expressed the average cost of a patient treated with mitomycin C for the first occurrence as a function of risk reduction, compared the average cost of a patient treated with BCG for the first occurrence of bladder cancer to the average cost of patient treated with mitomycin C, and solved this equation for risk reduction. This value represented the minimal treatment effect needed for the two options to be considered equal in terms of cost.

RESULTS

Use of an intravesical chemotherapeutic agent after TURB

Using the CCAE and Medicare databases from 1997 to 2004, we identified 16,748 patients whose claims listed bladder cancer as their primary or secondary diagnosis. From 1997 through 2004, 444,740 patients were estimated from SEER data to develop bladder cancer(30), and thus 4% of all newly diagnosed bladder cancers were captured by these databases. 14,677 (87.6%) subsequently underwent cystoscopy with biopsy or TURB of their bladder cancer (Table 3). Of these, only 49 (0.33%) received same or following day instillation therapy after their surgical procedure (Table 3). Most of these patients received mitomycin C (48 of the 49; 98%), while one patient (2%) received interferon alpha-2B. No patient received doxorubicin or thiotepa. When analyzed between 1997 and 2004, we detected no statistically significant changes in the annual rates of new diagnosis or treatment of bladder cancer, or the use of same-day intravesical therapy after TURB in this cohort (Table 3).

Economic benefits of instilling intravesical chemotherapy immediately after TURB

For the base case analysis, we assumed that the treatment was given for all newly diagnosed low risk patients (grades 1 and 2 and stages Ta and T1). By evaluating the literature, we estimated that bladder cancer patients without recurrence over 3 years will receive 10 surveillance cystoscopies (Figure 2). Based largely on AUA guidelines and the results of randomized clinical trials (20–26;28;29;31) patients who had recurrences underwent further resections and 6 weekly instillations of BCG with 3 maintenance instillations of BCG every 6 months for three years. Of those starting this course, we assumed that 25% would recur and undergo another TURB followed by instillations with BCG and alpha interferon. Of these patients, we assumed that 60% would recur. While treatment after a second or third recurrence in this brief a time is not standardized(20–26;28;29;31), to be extremely conservative, we assumed patients would subsequently not recur and be observed closely (i.e. frequent cystoscopies) (Figure 2). The second model used mitomycin C for the first recurrence, assuming 50% would recur during the period of follow-up(20;22–25;27;31–34). The second recurrence was treated with induction BCG and maintenance therapy if successful, and BCG + alpha interferon was used for the third recurrence. The anticipated efficacy of BCG and BCG + alpha interferon was assumed to be the same as in the first analysis. As with model 1, we assumed patients experiencing a third recurrence would not recur subsequently, and be managed by frequent monitoring. Because the literature is

equivocal regarding advantages of post-TURB single instillation intravesical therapy in patients with recurrent bladder cancers(7;29), we did not presume that patients with recurrences would receive this treatment(8;35).

With the utilization rates and outcomes discussed, we estimated that without same-day therapy and assuming BCG was administered at first recurrence (model 1) it would cost, on average \$5,760, to treat one patient with low-risk NMI bladder cancer for three years (Table 4). If all patients receive same day post TURB intravesical chemotherapy (we assumed mitomycin C would be used) the average per patient cost of three years of care is reduced to \$5,070 - a cost-savings of \$689 (12%) per patient for treatment with same-day intravesical chemotherapy compared with TURB alone. Nationally, this represents annual savings of \$24.8 million (60% of newly diagnosed bladder cancer per-year(1)(36)). A similar analysis was done with patients receiving mitomycin C on initial recurrence, BCG for the second recurrence and BCG and alpha interferon for the third. This would save \$538 per patient and save \$19.8 million nationally. (Figure 2, Table 4) Even if patients who failed the first BCG induction course were treated with a repeat course of BCG rather than BCG + alpha interferon, the savings for immediate post TURB intravesical instillation therapy would still be substantial: \$21.2 million if BCG was used for the first recurrence, and \$19.8 million if mitomycin C was (not shown).

Our threshold analysis demonstrated that the addition of single dose intravesical therapy after TURB must decrease recurrence by at least 7% (for the BCG assumption) to 10% (for mitomycin C) to cover the additional cost of services and medication.

DISCUSSION

Despite compelling evidence regarding the effectiveness of same-day intravesical therapy, between 1997 and 2004, only 0.33% of eligible U.S. patients received this treatment. We demonstrated that in addition to reducing the rate of bladder cancer recurrences, same-day intravesical therapy could also save \$538 to \$689 of medical expenses per patient or over \$15 to nearly \$25 million a year nationally.

The rationale behind single immediate instillation intravesical chemotherapy is that by reducing the rate of implantation, the likelihood of disease recurrence will decrease, as will the need for repeat TURBs and for longer courses of intravesical therapy. Table 1 reviews the results of randomized prospective trials of same-day intravesical instillation chemotherapy after TURB. This treatment has been shown to reduce recurrences by 17 to 44% compared with controls. A recent meta-analysis has confirmed that this treatment has decreased the risk of recurrence by 39% in patients with stage Ta and T1 bladder cancer(37).

The purpose of the analysis was to provide a conservative estimate of the economic benefit associated with using intravesical chemotherapy after TURB in the US. Since differences between countries in terms of health care systems (e.g., financing and organization) could have a substantial impact on the types of services patients receive, it is necessary to focus on a specific health care system. We chose the US health care system, and specifically the health insurer's perspective in order to notes the impact of this treatment on the overall cost of bladder cancer care. Similarly, we used Medicare reimbursement rates as a more conservative, lower bound estimate of the potential savings associated with the use of this intervention among both Medicare and privately insured patients. Another reason for using Medicare rates is that the average age of bladder cancer patients at the time of diagnosis is over 70 years(2).

Several assumptions were made in order identify our sample population. The first was that the 3-year recurrence rate of newly resected NMI bladder cancer is 40%. This has been

shown in a variety of follow-up studies of NMI bladder cancer as well as in placebo arms of randomized trials using BCG(20–26;28;29;31). Thus in building our model we assumed that 40% of patients with newly diagnosed and completely resected low risk bladder cancer will have recurrence during the 3-year follow-up period. We also assumed that there was no stage progression to muscularis propria invading disease. This was an extremely conservative estimate since in published series, stage progression has been reported to occur in 1% to 20% of patients with low risk NMI cancer. The cost of managing invasive bladder cancer is far greater than for NMI disease, and so failure to consider stage progression biased our cost projections against immediate post-TURB instillation therapy. At the time this study was carried out, the AUA had not established immediate intravesical therapy as standard of care but does recommend it as a therapeutic option(38), while the European Association of Urology had included it as standard of care for superficial bladder cancer(39). The recently revised AUA guidelines have now included it as an “option” (the weakest grade of guideline with the greatest flexibility in application) for care, although not as a “standard” or “recommendation”(40).

The next part of the model dealt with the treatment of patients with recurrences. Largely based on professional guidelines by the AUA and the results of randomized clinical trials(20–26;28;29;31) such patients underwent 6 weekly instillations of BCG with 3 maintenance instillations of BCG every 6 months for 3-years (although other forms of intravesical therapy could be used). Again based on published reports(20–26;28;29;31), we assumed that 25% of those receiving this course would recur and undergo further instillations with BCG and alpha interferon. Of those patients, we assumed that 60% would recur again(36;41). While at this point, the decision would be influenced by the patient’s co-morbidities and wishes and non-standard treatment by the treating physician, to be very conservative, we projected that there would not be further recurrences, and that only frequent cystoscopic monitoring would take place. This again reduced costs compared with the more aggressive therapies that would often be selected (e.g. cystectomy). Similarly, we modeled the cost if for the first recurrence six intravesical instillations of mitomycin C was used with an assumption that 50% receiving this treatment would recur(24;42). Subsequent recurrences were treated with BCG or BCG + alpha interferon. For both of these models we estimated and that were they to occur, all recurrences took place immediately after the index or subsequent TURB. While this is an oversimplification, the majority of recurrences take place within three to six months of the index TURB and over 70% within one year(40). Because most published trials and series end at the time of the initial recurrence, little data are available about the times of second and third recurrences. With longer intervals between recurrences, expenses would have changed little, as long as recurrences were treated as they were in the models. Additionally, because recurrences took place at the first cystoscopic evaluation after TURB, it is likely that standard intravesical therapy would have been recommended (because of the frequent recurrences), rather than simply continuing observational management. Using the above assumptions, we formulated models for the treatment of a patient with newly diagnosed NMI bladder cancer.

While cystectomy is sometimes performed for patients who recur after BCG treatments, this is almost exclusively reserved for patients with high grade disease. It is likely that very few (if any) patients would undergo it within the first three years of being diagnosed with low grade, NMI bladder cancer(28). Furthermore, we are unaware of any data addressing the circumstance (the proportion of patients with low risk newly diagnosed bladder cancer who are treated with BCG, recur after that treatment and who immediately go on to cystectomy) to guide our model. Both because such a circumstance is very rare and generally would occur beyond the time horizon of this study, it is not included in our model. Moreover, to be conservative, we assumed no grade (to high grade) or stage progression (to stage T2) would occur. These occur rarely in the population being considered(28). If either occurred,

cystectomy would be more likely. The huge cost associated with this procedure, which would be far more likely to occur in the observed arm, would further bias the results of the study in favor of immediate post TURB intravesical therapy. Lastly, we took a conservative estimate of 25% for the reduction in recurrence rate after immediate post-TURB intravesical instillation(37).

As with all studies using health-care databases, several factors should be considered when interpreting our findings. First, while the sample was drawn from more than 7 million lives, it may not be representative of the general population. There are regional biases in medical and urologic care(37;43), and it is possible that the geographic imbalance in our data may misrepresent what is occurring in the U.S. as a whole. However, given the only modest imbalance in geographic distribution, and the verified utilization of this database for other medical and oncologic conditions, this likely provides a relatively small bias, not explaining our results. Furthermore, although the databases allowed for the analysis of a large sample of patients across the U.S., only patients with commercial health coverage or private Medicare supplemental coverage were analyzed. Finally, these findings are based on retrospective analyses of claims data, and reliance on this data has limitations. For example, patients may receive treatment that is not submitted to their health plan for reimbursement, and thus is not included in claims data, and a small proportion of claims may be subject to coding errors. However, we believe our methodology to determine how often immediate post-TURB instillation therapy is used is reliable because it is administered by qualified medical personnel (and thus has a CPT code). Moreover because errors in billing that lead to problems in payments rarely go uncorrected, billing data are usually highly reliable(19).

Since we used Medicare reimbursement rates (which are usually lower than the rates reimbursed by private health plans) to estimate the cost of interventions, our estimates represent the lower bound of possible savings. However, the effectiveness of the same-day intravesical instillation chemotherapy may also vary depending on patient risk factors and medical histories. We demonstrated that as long as the intervention is at least 7% to 10% more effective than the TURB alone, post-TURB single intravesical instillation chemotherapy provides economic savings.

Why is the treatment performed so rarely? One reason is that while it is considered safe and well tolerated(5–10), there obviously are some patients with suspected bladder perforation or post TURB hematuria who should not receive it. Another reason is a technical matter involving dispensing and administering chemotherapy. Many American centers require chemotherapy nurses and ancillary staff to handle and instill these agents, preventing most operating or recovery room nurses from administering them. Currently, some urologists resort to instilling and overseeing the dispensation and handling themselves. The inconvenience of ordering, instilling, and waiting for the chemotherapy to dwell for 1–2 hours is, for a busy practitioner, clearly a deterrent to its use. Another barrier to its acceptance is the economic burden placed on the hospital. Currently, the additional expense of using intravesical chemotherapy in a hospital-based setting (e.g. operating room), are borne by the hospital without reimbursement for longer recovery room time, increased monitoring by specially trained nursing staff, and the expenses of disposing of the chemotherapeutic agent.

Another possible reason for not performing this treatment may be the way new scientific data are transmitted to, and incorporated into practice by physicians. Although, numerous clinical trials have shown its effectiveness, these data have not been widely accepted by U.S. urologists. Whether this is because they are unaware of the published data or because these trials have largely been performed outside the U.S. without the participation of American centers is unclear. American urologists may be resistant to embracing this approach without

validation by a large American study. The recent revision of AUA guidelines may have an influence on altering this practice, but this will not be ascertainable for several years.

CONCLUSIONS

Despite generalized acceptance of same-day intravesical instillation chemotherapy after TURB by urologists outside the U.S., this policy has not been embraced by American urologists. Reasons for this are unclear. Regardless of the reasons, we have shown that assuming conservative parameters for efficacy, adopting this policy would considerably lower the cost of caring for bladder cancer in the U.S.

Acknowledgments

Katia Noyes was supported in part by a K01 AG 20980 from the National Institute of Aging.

Ralph Madeb was supported in part by the Empire State Grant

Work also supported by the Ashley Family Foundation

Reference List

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics. *CA Cancer J Clin*. 2006; 56:106–30. [PubMed: 16514137]
2. Madeb R, Messing EM. Gender, racial and age differences in bladder cancer incidence and mortality. *Urol Oncol*. 2004; 22:86–92. [PubMed: 15082003]
3. Messing, EM. Urothelial tumors of the urinary tract. In: Walsh, PC., et al., editors. *Campbell's Urology*. Vol. 8. Philadelphia: WB Saunders; 2002. p. 2732-2784.
4. Klan R, Loy V, Huland H. Residual tumor discovered in routine second transurethral resection in patients with stage T1 transitional cell carcinoma of the bladder. *J Urol*. 1991; 146:316–8. [PubMed: 1856924]
5. Solsona E, Iborra I, Ricos JV, Monros JL, Casanova J, Dumont R. Effectiveness of a single immediate mitomycin C instillation in patients with low risk superficial bladder cancer: short and long-term followup. *J Urol*. 1999; 161:1120–3. [PubMed: 10081851]
6. Burnand KG, Boyd PJ, Mayo ME, Shuttleworth KE, Lloyd-Davies RW. Single dose intravesical thiotepa as an adjuvant to cystodiathermy in the treatment of transitional cell bladder carcinoma. *Br J Urol*. 1976; 48:55–9. [PubMed: 817761]
7. Oosterlinck W, Kurth KH, Schroder F, Bultinck J, Hammond B, Sylvester R. A prospective European Organization for Research and Treatment of Cancer Genitourinary Group randomized trial comparing transurethral resection followed by a single intravesical instillation of epirubicin or water in single stage Ta, T1 papillary carcinoma of the bladder. *J Urol*. 1993; 149:749–52. [PubMed: 8455236]
8. li-El-Dein B, Nabeeh A, el-Baz M, Shamaa S, Ashamallah A. Single-dose versus multiple instillations of epirubicin as prophylaxis for recurrence after transurethral resection of pTa and pT1 transitional-cell bladder tumours: a prospective, randomized controlled study. *Br J Urol*. 1997; 79:731–5. [PubMed: 9158511]
9. Shuin T, Kubota Y, Noguchi S, Hosaka M, Miura T, Kondo I, et al. A phase II study of prophylactic intravesical chemotherapy with 4'-epirubicin in recurrent superficial bladder cancer: comparison of 4'-epirubicin and adriamycin. *Cancer Chemother Pharmacol*. 1994; 35 (Suppl):S52–S56. [PubMed: 7994787]
10. Tolley DA, Parmar MK, Grigor KM, Lallemand G, Benyon LL, Fellows J, et al. The effect of intravesical mitomycin C on recurrence of newly diagnosed superficial bladder cancer: a further report with 7 years of follow up. *J Urol*. 1996; 155:1233–8. [PubMed: 8632538]
11. Cohen FJ, Neslusen CA, Conklin JE, Song X. Recent antihyperglycemic prescribing trends for US privately insured patients with type 2 diabetes. *Diabetes Care*. 2003; 26:1847–51. [PubMed: 12766121]

12. Hillman AL, Schwartz JS, Willian MK, Peskin E, Roehrborn CG, Oesterling JE, et al. The cost-effectiveness of terazosin and placebo in the treatment of moderate to severe benign prostatic hyperplasia. *Urology*. 1996; 47:169–78. [PubMed: 8607228]
13. Lyman GH, Berndt ER, Kallich JD, Erder MH, Crown WH, Long SR, et al. The economic burden of anemia in cancer patients receiving chemotherapy. *Value Health*. 2005; 8:149–56. [PubMed: 15804323]
14. Medicare Current Beneficiary Survey. Baltimore, MD: Center for Medicare and Medicaid Services; 2000.
15. Rajala P, Liukkonen T, Raitanen M, Rintala E, Kaasinen E, Helle M, et al. Transurethral resection with perioperative instillation on interferon-alpha or epirubicin for the prophylaxis of recurrent primary superficial bladder cancer: a prospective randomized multicenter study--Finnbladder III. *J Urol*. 1999; 161:1133–5. [PubMed: 10081854]
16. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Med Care*. 2005; 43:480–5. [PubMed: 15838413]
17. Freeman JL, Zhang D, Freeman DH, Goodwin JS. An approach to identifying incident breast cancer cases using Medicare claims data. *J Clin Epidemiol*. 2000; 53:605–14. [PubMed: 10880779]
18. Winkelmayer WC, Schneeweiss S, Mogun H, Patrick AR, Avorn J, Solomon DH. Identification of individuals with CKD from Medicare claims data: a validation study. *Am J Kidney Dis*. 2005; 46:225–32. [PubMed: 16112040]
19. Iezzoni, L. Risk Adjustment for Measuring Health care Outcomes. 3. Chicago: Health Administration Press; 2003.
20. Herr HW, Badalament RA, Amato DA, Laudone VP, Fair WR, Whitmore WF Jr. Superficial bladder cancer treated with bacillus Calmette-Guerin: a multivariate analysis of factors affecting tumor progression. *J Urol*. 1989; 141:22–9. [PubMed: 2908949]
21. Herr HW, Klein EA, Rogatko A. Local BCG failures in superficial bladder cancer. A multivariate analysis of risk factors influencing survival. *Eur Urol*. 1991; 19:97–100. [PubMed: 2022226]
22. Herr HW, Waringer DD, Fair WR, Oettgen HF. Bacillus Calmette-Guerin therapy for superficial bladder cancer: a 10-year followup. *J Urol*. 1992; 147:1020–3. [PubMed: 1552578]
23. Herr HW. Natural history of superficial bladder tumors: 10- to 20-year follow-up of treated patients. *World J Urol*. 1997; 15:84–8. [PubMed: 9144896]
24. Lamm DL, Blumenstein BA, Crawford ED, Crissman JD, Lowe BA, Smith JA, et al. Randomized Intergroup Comparison of Bacillus Calmette-Guerin Immunotherapy and Mitomycin C Chemotherapy Prophylaxis in Superficial Transitional Cell Carcinoma of the Bladder. *Urol Oncol*. 1995; 1:119–26. [PubMed: 21224104]
25. Lamm DL. Long-term results of intravesical therapy for superficial bladder cancer. *Urol Clin North Am*. 1992; 19:573–80. [PubMed: 1636241]
26. Lamm DL, Blumenstein BA, Crissman JD, Montie JE, Gottesman JE, Lowe BA, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol*. 2000; 163:1124–9. [PubMed: 10737480]
27. Lamm DL. Intravesical therapy for superficial bladder cancer: slow but steady progress. *J Clin Oncol*. 2003; 21:4259–60. [PubMed: 14581444]
28. Messing EM, Kim KM, Wilding G, et al. A randomized prospective phase III trial of difluoromethylornithine (DFMO) vs placebo (P) in preventing recurrence of completely.
29. Sylvester RJ, van der MEIJDEN AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol*. 2002; 168:1964–70. [PubMed: 12394686]
30. American Cancer Society. Statistics of Cancer Incidence 1997–2006. 2006.
http://www.cancer.org/docroot/STT/stt_0_2004.asp?sitearea=STT&level=1
31. Herr HW. Intravesical therapy. A critical review. *Urol Clin North Am*. 1987; 14:399–404. [PubMed: 3554695]

32. Herr HW, Laudone VP, Badalament RA, Oettgen HF, Sogani PC, Freedman BD, et al. Bacillus Calmette-Guerin therapy alters the progression of superficial bladder cancer. *J Clin Oncol.* 1988; 6:1450–5. [PubMed: 3418376]
33. Lamm DL. Bladder cancer: twenty years of progress and the challenges that remain. *CA Cancer J Clin.* 1998; 48:263–8. [PubMed: 9742893]
34. Lamm DL. Management of bladder cancer. *J Urol.* 2004; 171:2482–3. [PubMed: 15126880]
35. Zincke H, Utz DC, Taylor WF, Myers RP, Leary FJ. Influence of thiotepa and doxorubicin instillation at time of transurethral surgical treatment of bladder cancer on tumor recurrence: a prospective, randomized, double-blind, controlled trial. *J Urol.* 1983; 129:505–9. [PubMed: 6403716]
36. Messing EM, Madeb R, Young T, Gilchrist KW, Bram L, Greenberg EB, et al. Long-term outcome of hematuria home screening for bladder cancer in men. *Cancer.* 2006; 107:2173–9. [PubMed: 17029275]
37. Sylvester RJ, Oosterlinck W, van der MEIJDEN AP. A single immediate postoperative instillation of chemotherapy decreases the risk of recurrence in patients with stage Ta T1 bladder cancer: a meta-analysis of published results of randomized clinical trials. *J Urol.* 2004; 171:2186–90. quiz. [PubMed: 15126782]
38. Smith JA Jr, Labasky RF, Cockett AT, Fracchia JA, Montie JE, Rowland RG. Bladder cancer clinical guidelines panel summary report on the management of nonmuscle invasive bladder cancer (stages Ta, T1 and TIS). The American Urological Association. *J Urol.* 1999; 162:1697–701. [PubMed: 10524909]
39. Oosterlinck W, Lobel B, Jakse G, Malmstrom PU, Stockle M, Sternberg C. Guidelines on bladder cancer. *Eur Urol.* 2002; 41:105–12. [PubMed: 12074395]
40. Messing E, Kim KM, Sharkey F, Schultz M, Parnes H, Kim D, et al. Randomized Prospective Phase III Trial of Difluoromethylornithine vs Placebo in Preventing Recurrence of Completely Resected Low Risk Superficial Bladder Cancer. *J Urol.* 2006; 176:500–4. [PubMed: 16813878]
41. Madeb R, Messing EM. Long-term outcome of home dipstick testing for hematuria. *World J Urol.* 2008; 26:19–24. [PubMed: 18040694]
42. Duque JL, Loughlin KR. An overview of the treatment of superficial bladder cancer. Intravesical chemotherapy. *Urol Clin North Am.* 2000; 27:125–35. x. [PubMed: 10696251]
43. McNaughton CM, Barry MJ, Zietman A, Albertsen PC, Talcott JA, Walker CE, et al. United States radiation oncologists' and urologists' opinions about screening and treatment of prostate cancer vary by region. *Urology.* 2002; 60:628–33. [PubMed: 12385923]

Algorithm For Detection of Patients in MEDSTAT Database

Figure 1.
The algorithm to identify bladder cancer patients who received same day intravesical instillation of a chemotherapeutic agent post-TURB.

Figure 2.

Figure 2A. Algorithm For The Treatment Of the recurrence of Non-Muscle Invasive Bladder Cancer Over A 3-Year Period with BCG

Figure 2B. Algorithm for The Treatment of the recurrence of Non-Muscle Invasive Bladder Cancer Over A 3-Year Period with Mitomycin C

Table 1
World literature of randomized studies for immediate post-TURB intravesical instillation of a chemotherapeutic agent

Reference[/Year	Agent [dose]/Control	No. of Patients	Type of Patient	Stage	Interval of Follow-up	Recurrence Rate Outcome (Study arm versus control)				
Burnand [6]/1976	Thiotepa [90mg/100cc]/Observation	51	Unknown	Ta and T1	Recurrences at 2-5 year follow-up	57.9% versus 96.8% (P<.005)				
Zincke [35]/1983	Thiotepa [60mg/60ml H ₂ O] versus Doxir [50mg/60ml H ₂ O] versus H ₂ O (3-arm Study)	45	21% New	Ta, T1, Tis	Recurrence rate at 3-4 months		Tip	Doxir	H ₂ O	
			79% Recurrent				30%	32%	71%	
								43%	0%	43%
								26%	38%	81%
MCR/1985	Thiotepa [30mg/50ml]/Observation	256	100% New	Ta and T1	Recurrence rate at 2 years	35.4% versus 41.3% (p=0.7)				
MCR/1994	Follow up of Above study at 8.75y showed no difference of time to primary recurrence, recurrence rate, or failure free interval									
Oosterlinck [7]/1993	Epirubicin[80mg in50ccNS]/50cc of H ₂ O	399	80% New	Ta and T1	Recurrence rate per year	New: 15% vs 31% (P<.0001)				
			20% Recurrent			Recur: 26% vs 35% (P=0.38)				
			Overall			Overall: 17 versus 32% (P<.0001)				
Tolley [10]/1996	Mitomycin C [40mg/40ccH ₂ O]/Observation	306	100% New	Ta and T1	Recurrence rate at 2 years	42% versus 55% (p=.01)				
Ali-el-dein [8]/1997	Epirubicin [50mg/50ml NS]/Observation	109	55% New	Ta and T1	Recurrence rate at mean of 2.5 years	24% versus 52% (P<.002)				
Solsona [5]/1999	Mitomycin C [30mg/50ml of NS]/Observation	121	90% New	Ta and T1	Recurrence rate at 1 year	22% versus 59% (P<0.005)				
			10% recurrent							
			100% New			Ta and T1	Recurrence rate at 2 years	Epi	INF-α	Obs
Rajala [15]/1999	Epirubicin [100mg] versus Interferon α2b[50M units] versus Observation (3-arm study)	200	100% New	Ta and T1	Recurrence rate at 2 years	Overall				
							32%	62%	60% P<.05	
							27%	63%	55%	
					Multiple	56%	67%	2374%		

Table 2

Medicare Reimbursement rates for procedures related to the treatment and maintenance of bladder cancer.

	2005 Costs, (\$, USD)
Cystoscopy	196
TURB	1595
BCG Instillation	392
BCG and INF Instillation	1055
TURB with intravesical instillation	1856
Medication Cost (mitomycin C)	260

Counts of patients undergoing cystoscopy with biopsy (CPT code 52204) or transurethral resection of bladder tumor (CPT code 52224, 52234, 52235, 52240) among patients with newly diagnosed bladder cancer.

Table 3

Index Year	1997	1998	1999	2000	2001	2002	2003	2004	Total
Total No. of Intravesical Instillations Post TURB	1	7	5	3	9	9	9	6	49
Procedures Per Year	1066	1668	1416	1194	3124	2174	2254	1781	14677
% Of Instillations/Per Year	0.093	0.420	0.353	0.251	0.288	0.413	0.39	0.336	0.333

Table 4
Average 3-year cost of treating recurrent bladder cancer (for a cohort of 1,000 bladder cancer patients)

Model 1: Patients treated with BCG for first recurrence					
	No recurrence	One recurrence	Two recurrence	Three recurrences	
% of Patients, without Intravesical Instillation	60%	30%	4%	6%	
Costs, \$	1,176,420	2,947,974	615,993	1,019,704	
Average, \$	5,760				
↓ (Decrease in recurrence by 25%)					
% of Patients treated with Intravesical Instillation	70%	22.5%	3%	4.5%	
Cost, \$	1,372,490	2,210,981	461,994	764,780	
Average, \$ + 260 for instillation Mitomycin	5,070				

Model 2: Patients treated with Mitomycin C for first recurrence					
	60%	20%	15%	5%	
% of Patients, without Intravesical Instillation					
Costs, \$	1,176,420	1,102,168	1,947,687	927,981	
Average, \$	\$5,154				
↓ (Decrease in recurrence by 25%)					
% of Patients treated with Intravesical Instillation	70%	15%	11.25%	3.75%	
Cost, \$	1,372,490	826,626	1,460,765	695,918	
Average, \$ + 260 for instillation Mitomycin	\$4,616				