Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

Clinical Cancer Research

New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine

Jay B. Shah, David J. McConkey, and Colin P.N. Dinney

Abstract

Bladder cancer remains one of the most deadly and expensive diseases affecting modern society. The options currently available to patients with muscle-invasive bladder cancer have remained essentially unchanged for the last generation. As the roles for surgery and chemotherapy in the management of this lethal disease have become better defined, so too have the limitations of these two treatment modalities. Despite the lack of groundbreaking clinical advances over the past two decades, recent years have witnessed a notable increase in the amount of promising preclinical and early translational research that will greatly improve our understanding of the molecular underpinnings of bladder cancer. If this momentum in bladder cancer research continues to build, it is likely that in the next 5 to 10 years we will be able to achieve our goal of bringing bladder cancer treatment into the age of personalized medicine. *Clin Cancer Res; 17(9); 2608–12. ©2011 AACR.*

Background

Urothelial carcinoma of the bladder is the fifth most common cancer affecting the American population, with 70,530 new cases estimated for 2010 (1). It is also the ninth deadliest cancer in American men, with 14,680 deaths estimated for 2010. Urothelial cancers develop along two major tracks—noninvasive and muscle-invasive—that pose distinct challenges for clinical management. Patients with noninvasive urothelial carcinoma have a very high recurrence rate (~70–80%) and thus require frequent and prolonged cystoscopic surveillance, which makes bladder cancer the most expensive malignancy in terms of lifetime dollars spent per patient (2). For patients with muscle-invasive disease, the traditional standard of care has been radical surgery (cystoprostatectomy in men and anterior exenteration in women) with regional lymphadenectomy. For patients with advanced urothelial carcinoma of the bladder (defined as local extension to adjacent organs, regional lymphadenopathy, distant metastases, or disease recurrence after radical surgery), options for durable disease control are limited. For patients who present with metastatic disease or disease recurrence after radical surgery, the median survival has been estimated to be only slightly more than 1 year (3).

Authors' Affiliations: Department of Urology, University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding Author: Colin P.N. Dinney, Department of Urology, University of Texas, 1515 Holcombe Blvd, Unit 1373, Houston, TX 77030. Phone: 713-792-3250; Fax: 713-794-4824; E-mail: cdinney@mdanderson.org

doi: 10.1158/1078-0432.CCR-10-2770

Multimodality approach to bladder cancer

To improve the survival of patients with advanced bladder cancer, clinicians have integrated chemotherapy into various treatment paradigms. Early large-scale, randomized clinical trials showed that the combination of methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) had activity in patients with advanced bladder cancer (4). In the two decades following that discovery, many investigators have examined the role of chemotherapy in patients with clinically localized muscle-invasive bladder cancer (5, 6). Results have shown that administration of cisplatin-based chemotherapy in the neoadjuvant setting can prolong survival for patients with muscle-invasive bladder cancer. In a randomized controlled trial of patients with clinical stage $\geq$ T2 urothelial carcinoma of the bladder, the median survival for patients who received neoadjuvant chemotherapy prior to cystectomy was markedly greater than that for patients who proceeded directly to cystectomy (77 months versus 46 months; ref. 6). This improvement in survival was attributed to the fact that the cystectomy specimens from the combination-therapy group had a significantly greater likelihood of having no residual cancer compared with specimens from the surgery-alone group (38% versus 15%, $P < 0.001$).

Despite the existence of level 1 evidence showing that neoadjuvant chemotherapy is beneficial, this treatment remains grossly underutilized (7). Many clinicians counsel their patients to proceed directly to surgery, under the rationale that neoadjuvant chemotherapy overtreats many patients and that adjuvant chemotherapy can be selectively administered only to patients with unfavorable findings at cystectomy. The literature for adjuvant chemotherapy is less compelling than that for neoadjuvant chemotherapy; however, a direct, meaningful comparison between the two modalities has yet to be undertaken (8–13). Although it is not known whether there is a difference between the

Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

neoadjuvant and the adjuvant setting, it is becoming increasingly clear that chemotherapy does have a role in the treatment of clinically localized, muscle-invasive bladder cancer. The actual administration of systemic chemotherapy, rather than the specific timing of that administration, may be the most critical aspect (14).

To address concerns about overtreatment with nonselective use of neoadjuvant chemotherapy, the current practice at MD Anderson Cancer Center is to selectively administer neoadjuvant chemotherapy only to patients who have a palpable mass on examination under anesthesia, lymphovascular invasion in the transurethral resection of bladder tumor (TURBT) specimen, hydronephrosis, or aberrant histology (e.g., micropapillary, small-cell carcinoma, adenocarcinoma), that is, those patients who are thought to be at highest risk for harboring locoregionally advanced bladder cancer. Patients without any of these features are counseled to proceed to immediate cystectomy, and patients who are found to have pathologic upstaging at cystectomy are treated with adjuvant chemotherapy, without sacrificing survival (14). Patients who receive neoadjuvant chemotherapy and are found to have lymph-node–positive disease at cystectomy are also treated with adjuvant chemotherapy, albeit with a different regimen.

On the Horizon

The evolution of muscle-invasive bladder cancer from being a purely surgical disease to one that is best managed with a multimodal approach has been the key transformation in our conceptualization of this lethal cancer over the last decade. Our greatest challenges now are to (i) improve our ability to accurately stage patients (e.g., identify patients who need chemotherapy because cystectomy alone will be insufficient for cure), and (ii) improve our ability to predict which patients will respond to which chemotherapy regimens. In the current paradigm, there is no reliable way to distinguish between patients who have clinically occult, locoregionally advanced disease (and should therefore receive neoadjuvant chemotherapy) and those with truly localized, low-risk disease that would be best managed with immediate cystectomy. Various investigators are actively engaged in elucidating the biology of bladder cancer to aid in the development of biomarkers that can predict disease aggressiveness (to improve staging) and response to specific therapies (to allow for personalized treatment plans). The neoadjuvant paradigm described further below represents a promising step toward the personalization of therapy for invasive bladder cancer. Within the next 5 to 10 years, it is likely that we will develop accurate predictive markers of response to chemotherapy that will allow us to construct highly specific treatment plans tailored to each individual patient.

Understanding the biology of bladder cancer

Because it is well known that patients die not from the regional effects of bladder cancer within the pelvis but from the sequelae of metastatic disease, a major focus of research in this area has been to understand the basic biological mechanisms that promote cancer progression. Specifically, what is the biological switch that triggers bladder cancer cells to invade through the detrusor muscle and/or gain access to the lymphatic and vascular channels of the systemic circulation? What mechanisms allow tumor cells to colonize distant sites to establish metastases? Furthermore, what are the mechanisms that allow some cancers to be resistant to conventional chemotherapy?

Researchers have used different approaches to investigate the biological switch that allows bladder cancer progression. Brandt and colleagues at Johns Hopkins University focused on identifying bladder cancer stem cells in the basal cell compartment of the urothelial lining (15). This group posited that these cancer stem cells are ideally situated for escaping immune surveillance and surviving cytotoxic therapy by interacting with the neighboring stroma (16). Using preclinical models, Wu and colleagues (17) identified proteins that may be involved in both local escape from the bladder and metastatic colonization of distant sites. In a study using the UMUC-3 bladder cancer cell line, they showed that RalBP-1, an effector protein for the Ras pathway target RalA, is necessary for metastasis of human cancer cell lines. Additionally, they showed that tumor endothelin-1 facilitates metastatic colonization of the lung in a mouse xenograft model of bladder cancer (18). Other molecules that have been implicated in bladder cancer aggressiveness include src (which is paradoxically downregulated in muscle-invasive cancers), caveolin-1, galectin-1, p53, PTEN, and choline kinase-α (19–22).

Investigators have also used gene expression profiling to find molecular signatures that are predictive of patterns of metastasis and drug sensitivity. Building on previous findings that epithelial-to-mesenchymal transition (EMT) is involved in bladder cancer progression and metastasis, we used global gene expression profiling of human bladder cancer cell lines as well as primary patient tumors to define molecular signatures of tumor heterogeneity (23). Tumor cells naturally segregated into epithelial and mesenchymal subsets. The epithelial subset contained all of the nonmuscle-invasive tumors and approximately half of the muscle-invasive tumors. The epithelial subset expressed high levels of the p53 family member, p63, a marker of the basal stem cell compartment of the urothelium. It also contained all of the bladder cancer cell lines that were sensitive to inhibitors of epidermal growth factor receptor (EGFR) or fibroblast growth factor receptor-3. The mesenchymal subset was composed entirely of muscle-invasive tumors, and mesenchymal tumors tended to express lower levels of the PTEN tumor suppressor than did the epithelial tumors. These results are consistent with recent studies demonstrating that loss of PTEN drives the development of muscle-invasive disease in genetically engineered mice and is associated with muscle-invasive disease in patients (21). Preclinically, RNAi-mediated knockdown of the EMT-associated transcription factors Zeb1 and Zeb2 inhibits tumor cell invasion, whereas knockdown of the epithelial transcriptional regulator p63 increases Zeb1 expression

Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

in some bladder cancer cells and promotes tumor cell invasion (24). These findings are in keeping with the widely accepted two-track theory of bladder cancer development and suggest that EMT is a critical determinant of overall bladder cancer biology (25). Strikingly, however, we observed that high-level expression of p63 identified a particularly lethal subset of muscle-invasive bladder cancers, despite the apparent role of p63 in suppressing EMT. Our ongoing experiments are focused on more precisely defining the roles of p63 and EMT in muscle invasion and metastasis, and assessing their influence on sensitivity to conventional and investigational cancer therapies.

Improving selection of patients

Because it is likely that not all patients with invasive bladder cancer will benefit from neoadjuvant chemotherapy, better stratification of high- and low-risk cancers will be a key focus of emerging research efforts. Over the past two decades, our concept of staging has expanded beyond simple anatomical staging (e.g., examination under anesthesia or three-dimensional imaging) to incorporate adverse histologic features (e.g., variant histology or lymphovascular invasion) that reflect the virulent biology of bladder cancer. Although we have become modestly effective at distinguishing between high- and low-risk tumors, we still understage 40% of our patients, and 15% of these patients die of bladder cancer. To improve on these disappointing statistics, investigators are adopting a systems biology approach to incorporate molecular and genetic features into the staging paradigm and identify the relevant features of tumor biology that mediate bladder cancer pathogenesis. Such an understanding will allow for improved distinction between favorable and unfavorable cancers, and thus more informed and objective selection of neoadjuvant therapies.

The preliminary results of ongoing studies suggest that it is possible to refine our current staging scheme by integrating gene expression and microRNA profiling information with clinical parameters to classify risk. These results are being verified in larger cohorts of specimens from low-risk patients to determine whether it is possible to identify a signature from the arrays that can be used prospectively to help determine which patients will benefit most from neoadjuvant chemotherapy. Similarly, investigators are evaluating whether global gene expression patterns can identify patients who are likely to respond to specific therapies. Early findings suggest that, in addition to regulating disease progression, EMT also appears to be associated with sensitivity to cisplatin-based chemotherapy.

Smith and colleagues (26) developed a novel algorithm that may predict tumor cell sensitivity to various conventional and investigational agents. The coexpression extrapolation (COXEN) algorithm uses baseline gene expression profiling and drug sensitivity data from the NCI-60 panel of human cancer cell lines, and baseline gene expression profiling data from bladder cancer cell lines to isolate lists of coexpressed genes that are associated with sensitivity or resistance to a given drug. In several recent studies (26–28), investigators used COXEN to successfully predict tumor sensitivity to cisplatin-based therapy. Intriguingly, our preliminary data indicate that the expression of most of the COXEN-defined cisplatin resistance genes overlaps with molecular markers of EMT.

Neoadjuvant platform for development of personalized therapy

The efficacy of chemotherapy for more advanced bladder cancer has been stranded on a modest plateau for nearly a generation, with no seminal advances made since the advent of combination chemotherapy in the early 1980s. Reliable symptom palliation and routine prolongation of life have been achieved, but relapses are still swift, devastating, and all but inevitable. In this setting, there is a pressing need to expand the paradigm. Many of the newer biological agents have yet to be fully explored in bladder cancer. The neoadjuvant platform represents a very attractive method for developing personalized therapy for bladder cancer, and it may have implications for the treatment of other solid tumors. In comparison with other solid tumors that may require a diagnostic needle biopsy, bladder cancer allows for larger volumes of tumor to be obtained for diagnosis and research during staging cystoscopy and transurethral resection of tumor. After treatment is completed, additional tumor can be collected at a repeat cystoscopy or upon cystectomy, giving investigators the opportunity to evaluate the impact of a targeted agent on specific pathways. This may also allow us to explore avenues of tumor biology and pathways related to the chemosensitivity and chemoresistance of tumor cells. By developing new agents in the setting of patients with intact bladders, we can explore these agents and collect tissue specimens before and after therapy to measure receptor phosphorylation and other downstream targets, as well as response.

At MD Anderson Cancer Center, we have adopted a unique two-pronged paradigm to incorporate the study of novel agents both with and without cytoreductive chemotherapy (Fig. 1). The benefits of this strategy are clear: We can collect tissue before treatment by routine cystoscopy and then collect residual posttreatment tissue at cystectomy. This approach allows us to study the effects of novel agents on the downstream receptor pathways, in the hope of developing molecular markers that can predict response or resistance to treatment. Results from previous studies in the neoadjuvant setting suggested that overexpression of VEGF is associated with a higher rate of relapse despite the use of surgery and MVAC in these high-risk patients (29). On the basis of these data, we are currently conducting a trial in which dose-dense MVAC is combined with bevacizumab, with the goal of enhancing pathologic response (pT0) and improving survival of patients with locally advanced bladder cancer (30).

The second approach in our neoadjuvant paradigm is to study new agents in patients who may not require cytoreductive chemotherapy. Although it is clear that neoadjuvant chemotherapy improves the survival of patients undergoing cystectomy, the overall benefit is modest (6).

Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

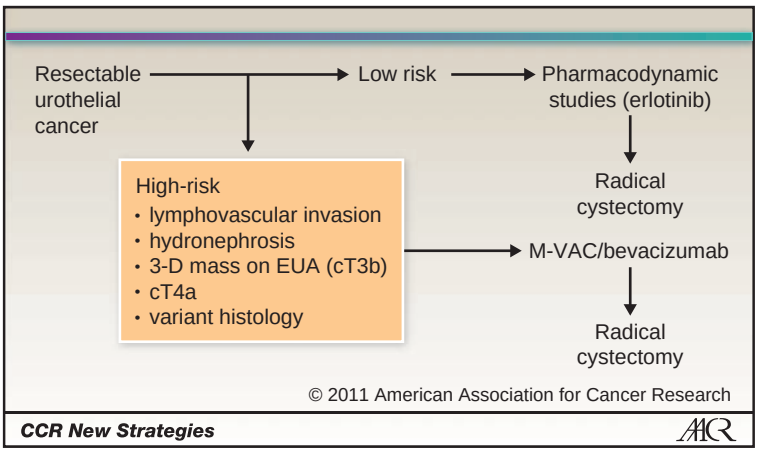

Figure 1. MD Anderson Cancer Center neoadjuvant paradigm for patients with invasive bladder cancer. All patients with invasive urothelial cancer are clinically stratified as either low risk or high risk for locoregionally advanced disease. Patients in the low-risk category (to whom chemotherapy is not typically administered) are offered enrollment in a single-agent study with a medication such as erlotinib. Erlotinib is given for 5 days prior to cystectomy. Pretreatment tissue (obtained at TURBT) and posttreatment tissue (obtained at cystectomy) are then used for pharmacodynamic and molecular profiling studies. Patients in the high-risk category are offered enrollment in clinical trials that call for the addition of a novel agent (e.g., bevacizumab) to conventional chemotherapy. For all patients with resectable invasive bladder cancer, the neoadjuvant paradigm allows for the testing of novel agents as well as the acquisition of pre- and posttreatment tissue without compromising patient care.

For patients with low-volume muscle-invasive disease or recurrent high-grade noninvasive or T1 tumors, there is a high likelihood of cure with cystectomy alone, with disease-specific survival at 10 years approaching 85% (C.P. N. Dinney, unpublished data). Traditionally, we have taken these patients to cystectomy first and then offered adjuvant chemotherapy selectively to patients with pathologic upstaging, with no sacrifice in survival. As part of our neoadjuvant paradigm, these patients are now offered inclusion in a novel proof-of-principle, phase II neoadjuvant trial of erlotinib to identify a signature of tumors that are likely to respond to EGFR-based therapy. We hypothesize that quantification of markers of EMT (e.g., e-cadherin, miR-200, and Zeb1/2) in pretherapy biopsies and correlation with changes in Ki-67 will allow us to prospectively identify tumors that are likely to respond to EGFR-based therapy. As in the neoadjuvant bevacizumab trial, tumor tissue is collected at baseline and residual tumor is collected at cystectomy. Knowledge gained from this trial may have a substantial impact by establishing a paradigm that sets the stage for personalized therapy for bladder cancer.

Conclusions

For clinicians and laboratory investigators alike, the ultimate goal of bladder cancer research is to reduce the morbidity and mortality of this aggressive disease through innovative, translational research in early detection, risk assessment, and personalized treatment. If we are to succeed, the foundation for this goal must be based on an improved understanding of the underlying genetic and molecular aberrations that contribute to the pathogenesis of this lethal disease. The significant advances made in bladder cancer research over the past decade have led to the development of molecular markers of risk, progression, and therapeutic response, as well as new therapeutic and preventive strategies based on this molecular information. The research advances on the horizon promise to simultaneously expand our armamentarium of treatment options for patients with invasive bladder cancer and improve our ability to select those patients who are most likely to respond to therapy. It is our hope that the momentum from these developments will boldly propel the field of bladder cancer therapy forward into the age of personalized medicine.

Grant Support

AstraZeneca, Schering Plough, Abbott, and Medtronic (C. Dinney).

Received February 24, 2011; accepted February 24, 2011; published OnlineFirst March 17, 2011.

References

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010;60:277–300.
2. Avritscher EB, Cooksley CD, Grossman HB, Sabichi AL, Hamblin L, Dinney CP, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. Urology 2006;68:549–53.
3. von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8.
4. Sternberg CN, Yagoda A, Scher HI, Watson RC, Herr HW, Morse MJ, et al. M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for advanced transitional cell carcinoma of the urothelium. J Urol 1988;139:461–9.

Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

5. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005;48:202–5, discussion 205–6.
6. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859–66.
7. David KA, Milowsky MI, Ritchey J, Carroll PR, Nanus DM. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data Base. J Urol 2007;178:451–4.
8. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005;48:189–99, discussion 199–201.
9. Freiha F, Reese J, Torti FM. A randomized trial of radical cystectomy versus radical cystectomy plus cisplatin, vinblastine and methotrexate chemotherapy for muscle invasive bladder cancer. J Urol 1996;155:495–9, discussion 499–500.
10. Lehmann J, Franzaring L, Thüroff J, Wellek S, Stöckle M. Complete long-term survival data from a trial of adjuvant chemotherapy vs control after radical cystectomy for locally advanced bladder cancer. BJU Int 2006;97:42–7.
11. Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. J Urol 1991;145:459–64, discussion 464–7.
12. Stöckle M, Meyenburg W, Wellek S, Voges G, Gertenbach U, Thüroff JW, et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. J Urol 1992;148:302–6, discussion 306–7.
13. Stöckle M, Meyenburg W, Wellek S, Voges GE, Rossmann M, Gertenbach U, et al. Adjuvant polychemotherapy of nonorgan-confined bladder cancer after radical cystectomy revisited: long-term results of a controlled prospective study and further clinical experience. J Urol 1995;153:47–52.
14. Millikan R, Dinney C, Swanson D, Sweeney P, Ro JY, Smith TL, et al. Integrated therapy for locally advanced bladder cancer: final report of a randomized trial of cystectomy plus adjuvant M-VAC versus cystectomy with both preoperative and postoperative M-VAC. J Clin Oncol 2001;19:4005–13.
15. Brandt WD, Matsui W, Rosenberg JE, He X, Ling S, Schaeffer EM, et al. Urothelial carcinoma: stem cells on the edge. Cancer Metastasis Rev 2009;28:291–304.
16. He X, Marchionni L, Hansel DE, Yu W, Sood A, Yang J, et al. Differentiation of a highly tumorigenic basal cell compartment in urothelial carcinoma. Stem Cells 2009;27:1487–95.
17. Wu Z, Owens C, Chandra N, Popovic K, Conaway M, Theodorescu D. RalBP1 is necessary for metastasis of human cancer cell lines. Neoplasia 2010;12:1003–12.
18. Said N, Smith S, Sanchez-Carbayo M, Theodorescu D. Tumor endothelin-1 enhances metastatic colonization of the lung in mouse xenograft models of bladder cancer. J Clin Invest 2011;121:132–47.
19. Canesin G, Gonzalez-Peramato P, Palou J, Urrutia M, Cordón-Cardo C, Sánchez-Carbayo M. Galectin-3 expression is associated with bladder cancer progression and clinical outcome. Tumour Biol 2010;31:277–85.
20. Hernando E, Sarmentero-Estrada J, Koppie T, Belda-Iniesta C, Ramírez de Molina V, Cejas P, et al. A critical role for choline kinase-alpha in the aggressiveness of bladder carcinomas. Oncogene 2009;28:2425–35.
21. Puzio-Kuter AM, Castillo-Martin M, Kinkade CW, Wang X, Shen TH, Matos T, et al. Inactivation of p53 and Pten promotes invasive bladder cancer. Genes Dev 2009;23:675–80.
22. Thomas S, Overdevest JB, Nitz MD, Williams PD, Owens CR, Sanchez-Carbayo M, et al. Src and Caveolin-1 reciprocally regulate metastasis via a common downstream signaling pathway in bladder cancer. Cancer Res 2011;71:832.
23. McConkey DJ, Choi W, Marquis L, Martin F, Williams MB, Shah J, et al. Role of epithelial-to-mesenchymal transition (EMT) in drug sensitivity and metastasis in bladder cancer. Cancer Metastasis Rev 2009;28:335–44.
24. Sayan AE, Griffiths TR, Pal R, Browne GJ, Ruddick A, Yagci T, et al. SIP1 protein protects cells from DNA damage-induced apoptosis and has independent prognostic value in bladder cancer. Proc Natl Acad Sci USA 2009;106:14884–9.doi:10.1073/pnas.0902042106 PubMed
25. Dinney CP, McConkey DJ, Millikan RE, Wu X, Bar-Eli M, Adam L, et al. Focus on bladder cancer. Cancer Cell 2004;6:111–6.
26. Smith SC, Baras AS, Lee JK, Theodorescu D. The COXEN principle: translating signatures of in vitro chemosensitivity into tools for clinical outcome prediction and drug discovery in cancer. Cancer Res 2010;70:1753–8.
27. Lee JK, Coutant C, Kim YC, Qi Y, Theodorescu D, Symmans WF, et al. Prospective comparison of clinical and genomic multivariate predictors of response to neoadjuvant chemotherapy in breast cancer. Clin Cancer Res 2010;16:711–8.
28. Smith SC, Baras AS, Dancik G, Ru Y, Ding KF, Moskaluk CA, et al. A 20-gene model for molecular nodal staging of bladder cancer: development and prospective assessment. Lancet Oncol 2011;12:137–143.
29. Inoue K, Slaton JW, Karashima T, Yoshikawa C, Shuin T, Sweeney P, et al. The prognostic value of angiogenesis factor expression for predicting recurrence and metastasis of bladder cancer after neoadjuvant chemotherapy and radical cystectomy. Clin Cancer Res 2000;6:4866–73.
30. Slaton JW, Millikan R, Inoue K, Karashima T, Czerniak B, Shen Y, et al. Correlation of metastasis related gene expression and relapse-free survival in patients with locally advanced bladder cancer treated with cystectomy and chemotherapy. J Urol 2004;171:570–4.

Published OnlineFirst March 17, 2011; DOI: 10.1158/1078-0432.CCR-10-2770

Clinical Cancer Research

New Strategies in Muscle-Invasive Bladder Cancer: On the Road to Personalized Medicine

Jay B. Shah, David J. McConkey and Colin P.N. Dinney

Clin Cancer Res 2011;17:2608-2612. Published OnlineFirst March 17, 2011.