

Online tools for patient counseling in bladder and kidney cancer—ready for prime time?

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Abstract: Gauging prognosis is a key element when facing treatment decisions in cancer care. Several prognostic tools, such as risk tables and nomograms are at hand to aid this process. In the context of patient-centered care, prognostic tools are of great interest to caregivers and -providers alike, as they can convey sizeable amounts of information and provide tailored, accurate estimates of prognosis. Given the rising number of prognostic tools in cancer care over the last two decades, and similarly, ever increasing presence of the Internet, we aimed to assess how this would translate into the availability of online tools for patient counseling. We used a modified systematic review to evaluate the web-based availability, format, and content of prognostic tools for bladder and kidney cancer care. Our search identified a total of twenty-three tools, offered by eight providers, which assessed a total of six (bladder cancer) and five (kidney cancer) different outcomes. Despite the restricted availability of online tools, we observed that the majority showed limited user-friendliness (including, for example, a statement/explanation of intended use, visualization of data, availability as application software for handheld devices). Only one tool included modifiable risk factors such as smoking behavior and body weight. Lastly, none of the tools incorporated genomic or molecular markers or treatment associated quality of life. Taken together, online tools for patient counseling in bladder and kidney cancer care are only beginning to align with the growing need in clinical reality. Further and future avenues include incorporation of health-related quality of life as well as genomic and biomarkers into prediction tools.

Keywords: Urinary bladder neoplasms; kidney neoplasms; patient-centered care; prognosis

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Introduction

Estimating prognosis is a key element throughout the cancer continuum and as such the foundation of treatment decisions that physicians and their patients have to face. In addition to the challenge of gauging prognosis, advances in the medical field have led to multiple treatment options, among which patients and their families have to choose—adding to the complexity of information to process and

thereby creating a potential barrier for non-medically trained subjects. Formerly, the doctor-patient relationship placed physicians in a paternal role whereas patients assumed a rather passive, dependent role when facing clinical decisions (1). However, lack of patient involvement in treatment decision is a major risk factor for regret of treatment choice (2) and throughout the last four decades the idea of *patient-centered care* or *patient-centeredness* has emerged—a concept which takes into consideration

personal preferences, needs, and values, and actively engages patients in clinical decision-making (3). A vast body of evidence supports this approach and has demonstrated that patient-centered care improves disease-related outcomes and quality of life (3). Central to the concept of patient-centeredness is the idea of shared-decision making, which in turn necessitates conveying a great volume of information to the patient (4). Providers of cancer care can rely on a number of counseling tools to provide such information. These include estimates and recommendations based on their own clinical experience and intuition, scientific publications (i.e., data from clinical trials), cancer registry data [i.e., Surveillance Epidemiology and End Results (SEER)], look-up tables, and prediction models such as nomograms. The latter hold distinct advantages: They perform with greater accuracy than physicians' estimations or stage based predictions. Moreover, can they integrate multiple disease and patient characteristics and thereby provide patient-tailored estimates of a given outcome (5).

With the availability of the Internet to an ever-increasing patient population, online access to counseling tools, such as prediction models and registry data is gaining in importance. In fact, it has been estimated, that 4.5% of all web-based search queries are conducted for health-related issues (6) and that 62–80% of cancer patients are interested obtaining web-based information (7). While online prognostic tools are readily available in breast and colon cancer (8,9) their availability to patients with bladder and kidney cancer has not been evaluated to date. The aim of this semi-systematic review, therefore, was to evaluate the availability of online prognostic tools intended for patient use in bladder and kidney cancer, as well as to describe their content and format.

Methods

First, a nonsystematic literature search was conducted using the MEDLINE/PubMed database to identify original articles, review articles and editorials. Searches were limited to the English language, and used the keywords *urothelial carcinoma; transitional cell carcinoma; muscle-invasive, non-muscle invasive bladder cancer; kidney cancer; renal cell carcinoma* in combination with *prognostic factor; predictive tool; nomogram; risk stratification; survival; recurrence*. All abstracts were reviewed and the corresponding full-length articles for those that were most relevant to each subsection were analyzed. Articles written before 1995 were excluded from analysis. Secondly, we performed an Internet search, using

the search engine Google and employed similar terms as in our literature search. For each search, the first five pages of results for relevant tools were reviewed. Predictive tools identified in this search approach were only selected for further review if they were accessible in an online format.

Results

Bladder cancer

With an estimated 79,030 new diagnoses and 16,870 deaths in 2017, bladder cancer is the 5th most common cancer in the U.S. alone and conveys the highest mortality among urological malignancies (10). Non-muscle invasive (NIMBC) and muscle-invasive (MIBC) disease vary in prognosis and generally are amenable to several treatment regimens. Contrary, in the metastatic setting of bladder cancer, therapeutic options are limited at poor prognosis with little change seen over the last decades (11).

Cancer registry data

The SEER program, sponsored by the National Cancer institute, consists of multiple statewide tumor registries that cover cancer incidence and survival of approximately 28% of the US population (12). Since its inception in 1973, these population-based data are made available to the public on an annual base and in the current web-based format offer a wide array of information to patients (*Table 1*). These include information about the incidence, as well as the relative overall and stage-specific (defined as in situ, localized, regional, distant) survival, stratified by gender, age, and race (available as "statistical summaries") (35). In addition to these cancer statistics, the website offers several interactive tools, such as "know your chances", that offer survival estimations in the context of competing risks, and under stratification of age, gender and race, albeit without stage-specific stratification (35).

Overall disease risk

Our search identified one predictive model for the overall risk of BC that has been made available in a patient-friendly, web-based format. The Washington University School of Medicine/Harvard Cancer Risk Index (13) is based on a simple scoring system in dichotomous format (*Table 1*). Based on individual risk factors, such as age, family and smoking history, and environmental exposure (including exposure to aromatic amines and water chlorination) a score is built. The score is then compared to the population

Table 1 List of prognostic tools made available to bladder and kidney cancer patients

Outcome/cancer entity	Prediction form	Details	Tool provider	Web address
Bladder/kidney cancer				
Cancer specific survival	Risk table	Probability of overall survival based on gender, age, race and disease stage (<i>in situ</i> , localized, regional, distant). Combined numerical output/visualization aid (icon array/scale)	National Cancer Institute	https://seer.cancer.gov/
Cancer specific and other cause mortality	Risk table	Probability of cancer specific and other cause mortality, based on gender, age, race, competing risk, and disease stage (<i>in situ</i> , localized, regional, distant). Combined numerical output/visualization aid (icon array/scale)	National Cancer Institute	https://knowyourchances.cancer.gov/
Bladder cancer				
Disease risk				
Colditz <i>et al.</i> 2000 (13)	Risk score	Offers simple estimation of cancer risk relative to US population average	Siteman Cancer Center, Washington University School of Medicine/ Harvard School of Public Health	http://www.yourdiseaserisk.wustl.edu/
NMIBC				
Prediction of disease recurrence and progression				
Sylvester <i>et al.</i> 2006 (14)	Risk table	Probability of disease recurrence and progression at 1 and 5 years based on clinicopathological features. Available in App format	Fox Chase Cancer Center, European Organization for Research and Treatment of Cancer	http://labs.fccc.edu/nomograms http://eortc.org/tools
Prediction of overall mortality				
Cambier <i>et al.</i> 2016 (15)	Nomogram	Probability of overall survival based on age and tumor grade. Combined numerical output/visualization aid (scale)	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
MIBC				
Prediction of non-organ confined disease and/or nodal positive disease				
Karakiewicz 2006 (16)	Nomogram	Based on age and pathological features at TURB. Combined numerical output/visualization aid (scale)	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Prediction of disease recurrence and survival following radical cystectomy				
Bochner 2006 (17)	Nomogram	5-year recurrence free survival based on clinicopathologic features	Memorial Sloan Kettering Cancer Center	https://www.mskcc.org/nomograms
		Combined numerical output/visualization aid (icon array, scale)	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
		Numerical output	Cleveland Clinic	http://riskcalc.org:3838/bladderCancer/
Karakiewicz 2006 (18)	Nomogram	Risk of recurrence at 2, 5, and 8 years based on clinicopathological features including receipt of chemotherapy/ adjuvant radiation. Combined numerical output/visualization aid (graph)	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Shariat 2006 (19)	Nomogram	Chance of overall and cancer specific survival at 2, 5, and 8 years based on clinicopathological features including receipt of chemotherapy/adjuvant radiation. Combined numerical output/visualization aid (graph)	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Lughezzani 2011 (20)	Risk table	Prediction of cancer specific and other-cause mortality based on age, pathological tumor and nodal stage. Numerical output	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms

Table 1 (continued)

Table 1 (continued)

Outcome/cancer entity	Prediction form	Details	Tool provider	Web address
Kidney cancer				
Disease risk				
Colditz <i>et al.</i> 2000 (13)	Risk score	Offers simple estimation of cancer risk relative to US population average	Siteman Cancer Center, Washington University School of Medicine/ Harvard School of Public Health	http://www.yourdiseaserisk.wustl.edu/
Localized disease				
Lane 2007 (21)	Nomogram	Preoperative nomogram used to estimate the chance that an enhancing renal mass is benign	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Kutikov 2011 (22)	Nomogram	Preoperative nomogram to predict malignancy or high grade in an enhancing renal mass	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Raj 2008 (23)	Nomogram	Preoperative nomogram for predicting freedom from metastatic recurrence within the first 12 years following radical or partial nephrectomy	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Kattan 2001 (24)	Nomogram	Prediction of 5-year recurrence probability following surgery	Memorial Sloan Kettering Cancer Center, Cleveland Clinic Foundation	https://www.mskcc.org/nomograms/renal/post-op , http://riskcalc.org/KidneyCancer/
Sorbellini 2005 (25)	Nomogram	Prediction of 5-year recurrence probability following surgery specifically for clear cell kidney cancer	Cleveland Clinic Foundation	http://riskcalc.org/
Karakiewicz 2007 (26)	Nomogram	Prediction of 1-, 2-, 5-, and 10-year disease-specific survival after surgery	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Kutikov 2010 (27)/2012 (28)	Nomogram	Disease-specific mortality in kidney cancer, with or without comorbidities	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Frank 2002 (29)	Score	Cancer Specific Mortality after nephrectomy for clear cell renal cell carcinoma	MDcalc	https://www.mdcalc.com/ssign-score-renal-cell-carcinoma-rcc
Metastatic disease				
Motzer 1999 (30)	Score	Predictive model for survival in patients with metastatic RCC based on risk stratification	Fox Chase Cancer Center/MDcalc	http://labs.fccc.edu/nomograms/ https://www.mdcalc.com/memorial-sloan-kettering-cancer-center-mskcc-motzer-score-metastatic-renal-cell-carcinoma-rcc
Mekhail 2005 (31)	Score	Predictive model for survival in patients with metastatic RCC based on risk stratification	MDcalc	https://www.mdcalc.com/mekhail-extension-motzer-score
Heng 2009 (32)	Score	Determines overall survival in patients treated with VEGF-targeted therapy	MDcalc	https://www.mdcalc.com/heng-score-metastatic-renal-cell-carcinoma-rcc-prognosis
Eggener 2006 (33)	Nomogram	Predictive model for survival in patients who have experienced a recurrence following nephrectomy	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms
Motzer 2008 (34)	Nomogram	Nomogram predicting 12-month progression-free survival in patients with metastatic clear cell RCC who receive sunitinib	Fox Chase Cancer Center	http://labs.fccc.edu/nomograms

average to provide the user with a relative risk estimate (“low”, “average”, “high”). This comparison is based on Surveillance Epidemiology and End Results (SEER) published data. A limitation includes the lack of providing absolute risk estimates. Further, this model was developed and validated in a US population and may therefore not be applicable in a European cohort.

Non-muscle invasive bladder cancer (NMIBC)

The European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Cancers Groups has developed a scoring system and risk tables to predict the 1- and 5-year probabilities of disease recurrence and progression in patients diagnosed with pathological Ta/T1 NMIBC (*Table 1*). The model was developed using previous trial data of 2,596 patients and incorporates six clinicopathological features: Tumor stage and grade, number of tumors, tumor size, concomitant Carcinoma in situ, and history of prior disease recurrence (14). To date, the model has been externally validated in a number of cohorts and has been incorporated into international guidelines (36,37). Further, the risk-tables are available as application software (App) for handheld devices. Notably, the model has some distinct limitations, which mainly pertain to the accrual period of patients (1979 to 1989), which is not reflective of current standards of treatment. For example, a second look transurethral resection of the bladder was not performed, and fewer than 10% of the patients received immediate intravesical instillation therapy. Consequently, the model tends to overestimate the risk of disease recurrence and progression (38).

In an effort to address these shortcomings, a recent report has developed a nomogram and a risk grouping system for NMIBC in patients that were treated with 1–3 years of intravesical Bacillus Calmette-Guerin (*Table 1*). The model was developed in two contemporary EORTC trial cohorts [1992–2013] to predict disease recurrence, progression, disease-specific and overall survival and subsequently (15). The according nomogram consists of the two factors age and grade and predicts 1- and 5-year survival probability (15). Limitations include the lack of patients with Carcinoma in Situ as well as pending external validation.

Muscle-invasive bladder cancer (MIBC)

Prediction of non-organ confined disease

Karakiewicz *et al.* developed a preoperative nomogram to predict advanced pathological disease stage and presence of lymph node metastasis at the time of radical cystectomy (16).

The model was developed in a cohort of 731 patients and incorporates age, stage, grade, and presence of carcinoma *in situ* at transurethral resection of the bladder, and further has recently been externally validated (39) (*Table 1*).

Prediction of disease recurrence and survival following radical cystectomy

Our web search identified four nomograms that predict survival in patients undergoing radical cystectomy and which have been made available in a patient-friendly web format (*Table 1*) (17–20). The International Bladder Cancer Nomogram Consortium (IBCNC), developed a postoperative nomogram predicting the 5-year risk of disease recurrence following radical cystectomy and pelvic lymph node dissection (17). The nomogram was developed in a multicenter cohort of more than 9,000 patients and has subsequently been externally validated in a large European cohort (40). Variables included are gender, age, pathological tumor stage and grade, histologic type (transitional cell and squamous cell carcinoma, adenocarcinoma), pathological nodal stage, and time from diagnosis of disease to radical cystectomy. Similarly, Karakiewicz *et al.* (18) in a multicenter cohort of 728 patients developed a nomogram to predict disease recurrence after radical cystectomy with bilateral lymphadenectomy. The model differs from the IBCNC in that it requires the presence of lymphovascular invasion or carcinoma in situ, as well as adjuvant chemoradiotherapy in addition to a pathological tumor and nodal stage. Shariat *et al.* (19) relying on the same cohort, developed a nomogram to predict all-cause and cancer-specific survival at 2, 5, and 8 years after radical cystectomy. External validation of both models is pending to date.

Lastly, Lughezzani *et al.*, (20) using the SEER registry, developed competing risk tables to provide cancer-specific and overall mortality, based on stratification by pathological tumor and nodal stage, as well as age at surgery.

Kidney cancer

Kidney cancer is the 10th most common cancer overall and affects nearly 63,330 patients in the US alone per year (10). The differentiation between localized and metastatic disease is crucial for making treatment decisions. Especially for metastatic disease stages, treatment options have expanded tremendously over the past decade. Within this environment, urologists have to increasingly rely on tools to counsel their patients.

Localized kidney cancer

These days, localized kidney cancer is almost exclusively diagnosed at an asymptomatic stage through the increased use of radiographic imaging. These incidental lesions pose a challenge for radiologists and urologists alike: First, imaging is not perfectly reliable while providers and patients need an accurate estimation of malignant potential. Second, patients are inherently eager to know about potential risks of local or systemic recurrence before and after surgery.

Preoperatively, to estimate the chance of a radiologic lesion to be malignant, Lane *et al.* proposed a model based on age, radiographic tumor size, smoking history, symptoms at presentation and gender. Although parameters from 862 patients were considered, the nomogram had a relatively low concordance index of 0.64 (21). Kutikov and colleagues evaluated whether radiographic features of renal masses could predict tumor pathology. In a comprehensive institutional cohort of 525 patients, they found that the RENAL nephrometry score (41) could quantitate the preoperative likelihood of malignant and high-grade pathology (22). Based on readily available preoperative parameters (gender, mode of presentation, radiographic lymphadenopathy, radiographic evidence of necrosis and tumor size), Raj used a multi-institutional cohort of >2,000 patients with either radical or partial nephrectomy to help counsel patients regarding their 12-year metastasis-free survival (23).

Similarly, there exist several prognostic calculators after surgery for kidney cancer. The Karakiewicz nomogram helps estimate cancer-specific survival 1-, 2-, 5-, and 10-year after local surgery by utilizing pathological (T stage, nodal status, presence of metastases, tumor size, tumor grade) and clinical (symptoms at presentation) (26). Kattan *et al.* (24) proposed a nomogram based on histological (chromophobe, conventional, papillary, none), clinical symptoms (none, incidental, local, systemic), tumor stage (AJCC Version 5) to calculate the 5-year recurrence free survival after surgery. The same group proposed a nomogram exclusively for clear cell renal cell carcinoma, the most common subtype, in 2005 (25). Parameters include tumor size in centimeter, the pathological stage according to the 2002 TNM classification, pathological grading, necrosis, vascular invasion and stage at presentation (incidental, local, metastatic). The latter nomogram was updated in 2016 and validated in a larger cohort (42). In elderly patients, death from disease is more unlikely than death from other causes. A simple nomogram consisting of information about race, gender, age and tumor size is available to calculate

the competing risk unadjusted (27) or adjusted for relevant comorbidities (28). In clear cell kidney cancer, the stage, size, grade, and necrosis (SSIGN) score (29) is used to estimate cancer-specific survival after radical nephrectomy. Its reliance on the overcome 2002 TNM classification hampers its current clinical applicability.

Metastatic disease

Patients with metastatic kidney cancer have an array of treatment options currently available. However, until the middle of the last decade, traditional immunotherapy was the treatment of choice. The Motzer score was developed to model survival in metastatic kidney cancer in these patients and is traditionally based on the levels of LDH, Hb, corrected serum calcium, Karnofsky performance status and a disease-free interval of <1 year (30). In the Mekhail extension, performance status is dropped with the addition of prior radiation treatment and the number of metastasis (≥ 2) (31). With similar parameters, Eggener *et al.* have developed a nomogram to estimate survival in patients with a recurrence following nephrectomy (33). Probably the most useful score in the treatment of metastatic renal cell carcinoma in the current treatment environment is the Heng score. Developed in a large, multi-institutional cohort, it uses the time from diagnosis to the initiation of systemic therapy, the performance index, Hb, Calcium, Neutrophil count and platelet count to estimate overall survival. Most importantly, it was developed in a cohort of patients treated with VEGF-therapy, specifically (32). Another useful application was described by Motzer *et al.* in 375 patients on Sunitinib therapy for metastatic kidney cancer. 12-month progression-free survival is calculated using the backbone of the traditional Motzer score (Hb, time to treatment, LDH and corrected calcium) with the addition of a number of metastatic sites, the presence of lung or liver metastases, ECOG PS, thrombocytosis, Alkaline Phosphatase and prior nephrectomy (34).

Uncharted territory of online tools for patient counseling with kidney cancer

At the dawn of personalized medicine, tremendous opportunities and challenges lie ahead. An interesting online tool without current clinical evidence might be the Genetic Data Commons Data Portal of the National Institute of Health. In this robust data-driven online repository, cancer researchers and bioinformaticians can browse through over 1,600 kidney cancer cases with various information on genes, alterations and gene mutations

(<https://portal.gdc.cancer.gov/>). Another source, which by now is mainly research-driven, is the clear cell renal cell carcinoma metabolomics data explorer as provided by the MSKCC (<http://sanderlab.org/kidneyMetabProject/>). Metabolograms are a visual tool for exploring metabolic pathways using both gene expression and metabolite abundance data. In an app, users can review metabolite data between tumor and normal samples, or see how the metabolic data line up against the gene expression data obtained from the Cancer Genome Atlas (<https://cancergenome.nih.gov/>). Ultimately, these tools can help identify new treatment targets.

Discussion

Prognostic tools pose a valuable option to facilitate shared decision-making throughout the cancer continuum, as they incorporate individual patient, disease, and possibly treatment characteristics to provide tailored estimates of prognosis. While such tools are readily available in breast and colon cancer treatment, their availability for bladder and kidney cancer has not been evaluated. Therefore, this semi-systematic review aimed to identify and describe predictive tools for patients undergoing treatment for the latter two malignancies, available in a web-based format.

Our search identified a total of twenty-three tools, which assessed a total of six (bladder cancer) and five (kidney cancer) different outcomes. These tools were developed in a number of populations, ranging from single-/multi-institutional to large population-based datasets such as SEER. Interestingly, despite the relative variability in the number of tools, the variability in terms of providers was limited to eight. While we find this indicative of a relative lack of availability of online tools, we also observed that among these providers, “user-friendliness” differed, which could particularly affect patients with limited health literacy/numeracy. For example, while all websites provided legal disclaimers for the intended use, only three providers offered an introductory/explanatory page to provide a description of the tools intent, data elements used, and outcomes provided. In this regard, only one of the tools was made available in an app format that would support its use on a handheld device, despite evidence of a growing desire for such applications among patients and providers (43).

Aside from a lack of user-availability and -friendliness we observed that none of the tools incorporated genomic or molecular markers, which we feel will be a critical future step as personalized medicine is evolving. Further, only

one of the tools incorporated modifiable risk factors, such as smoking behavior or weight loss into prognosis (13). However, given the “teachable moment” associated with cancer diagnosis, incorporation of modifiable risk factors could function as a motivator of behavioral change (8). Lastly, none of the tools identified in this review used quality of life or adverse treatment effects as a predicted outcome. Yet, the prevalence of cancer survivors has been rising throughout recent decades and as such, treatment associated quality of life is emerging as valuable measurement of treatment success (44). For example, studies among patients receiving treatment for head and neck cancer show that almost a quarter of patients rank cure as secondary to functional outcome and health-related quality of life (45).

The current review has to be considered within its limitations, such as its non-systematic approach. In addition, we restricted our search to tools available in web-based format. Taken together, patients and care providers in bladder and kidney cancer care can rely on over 20 different online tools to provide estimates of prognosis and to aid clinical decision making. However, limited variability in providers and user-friendliness, lack of app-based formats, and incorporation of outcomes other than survival demonstrate that online tools for patient counseling in bladder and kidney cancer care are only beginning to align with a growing need in clinical reality. Further and future avenues include incorporation of health-related quality of life as well as genomic and biomarkers into prediction tools.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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