Application of Artificial Intelligence to the Management of Urological Cancer

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Purpose: Artificial intelligence techniques, such as artificial neural networks, Bayesian belief networks and neuro-fuzzy modeling systems, are complex mathematical models based on the human neuronal structure and thinking. Such tools are capable of generating data driven models of biological systems without making assumptions based on statistical distributions. A large amount of study has been reported of the use of artificial intelligence in urology. We reviewed the basic concepts behind artificial intelligence techniques and explored the applications of this new dynamic technology in various aspects of urological cancer management.

Materials and Methods: A detailed and systematic review of the literature was performed using the MEDLINE® and Inspec® databases to discover reports using artificial intelligence in urological cancer.

Results: The characteristics of machine learning and their implementation were described and reports of artificial intelligence use in urological cancer were reviewed. While most researchers in this field were found to focus on artificial neural networks to improve the diagnosis, staging and prognostic prediction of urological cancers, some groups are exploring other techniques, such as expert systems and neuro-fuzzy modeling systems.

Conclusions: Compared to traditional regression statistics artificial intelligence methods appear to be accurate and more explorative for analyzing large data cohorts. Furthermore, they allow individualized prediction of disease behavior. Each artificial intelligence method has characteristics that make it suitable for different tasks. The lack of transparency of artificial neural networks hinders global scientific community acceptance of this method but this can be overcome by neuro-fuzzy modeling systems.

Key Words: bladder, bladder neoplasms, prostate, prostatic neoplasms, neural networks (computer)

Improvements in the understanding and treatment of cancer mean that today clinicians often must predict disease behavior in an individual to tailor management. This is well illustrated in the field of urological cancer, in which localized CaP is often overtreated and delays in radical treatment for bladder UC may worsen prognosis. Improvements in the prediction of disease behavior can be made by the acquisition of new parameters, such as molecular biomarkers, or by better interpretation of current data. While numerous novel biomarkers have been described, few appear sufficiently reliable for routine use. In contrast, robust improvements in data interrogation for disease prediction have been reported by several groups with the application of AI. These techniques use complex mathematical models based on the human neuronal structure and thinking. They are capable of generating data driven models of biological systems without making assumptions based on statistical distributions. However, the lack of transparency of many AI methods has led to skepticism regarding their results.[1–3] We reviewed the basis and application of AI modeling techniques currently applied in urological cancer.

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BASICS OF MACHINE LEARNING AND AI

While human learning is difficult to define, a machine learns when it changes its structure, data or program in response to external information. In such a manner the machine is expected to improve future performance. Machine learning can be applied to any situation in which repetitive system data can be obtained, whether biological or mechanical. Learning can be used to train a machine, so that it optimizes its rule base in a model and then new parameters maybe tested in that model. The application of machine learning is termed AI. It can be described according to its design as Bayesian networks, expert systems, ANNs, modeling systems (NFMs) and decision trees. Each method has strength and weaknesses, of which the choice depends upon the task at hand (see Appendix).

Bayesian Networks

Probabilistic DSSs are a recent generation of systems that are capable of modeling real world problems using theoretically sound and practically invaluable methods of probability and decision theory. Based on graphic representations these systems enable combining expert opinions with frequency data, gathering, managing and processing informa-

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tion to arrive at intelligent solutions.[4] They allow the introduction of prior knowledge into data analysis. Classic inferential models do not permit this knowledge to prevent the inclusion of extraneous data that might skew the calculation. While this exclusion is statistically rigorous, there are instances when the use of prior knowledge could improve the analytical process. Bayesian networks are useful for inferential exploration of undetermined relationships among variables and descriptions of these relationships. In the former case raw computational power can be brought to bear on a problem.[4] While such a process is computationally intensive and complex, its benefits are evident in the ability to describe the discovered network in the future. The calculation of any probability branch of the network can then be calculated in linear time. DSSs are applicable in medicine for diagnosis, prognosis and therapy planning. An example is a medical diagnostic system, based on a Bayesian network model, which aids physicians in the diagnosis of liver disorders.[5] The structure of the model consists of variables elicited from physicians and its numerical parameters learned from a database of patient cases.

Expert Systems

An expert system is a computer program that contains subject specific knowledge from human experts. The commonest is a program made up of rules that analyze information (supplied by the user) about a specific problem. The program also provides mathematical analysis of the problem(s) and depending on their design recommends a course of action. The system uses machine based reasoning capabilities to reach conclusions. Medical expert systems have evolved to provide physicians with structured questions and responses in specialized domains, and provide the most accurate conclusions to be drawn from the answers of the user. Although the physician is free to select any of the offered choices, they are limited by the input of the expert and the program is unable to accommodate new questions or data. It is for this reason that open system programs have been developed to meet new user needs.[6] Expert systems were first applied to clinical DSSs and they can be used for numerous applications (see Appendix).[6]

ANNs

ANNs are powerful, nonlinear statistical paradigms for recognizing complex patterns. They are able to maintain accuracy when some data required for complete network function are missing. They have been previously reviewed in detail[7] and used widely in urological oncology (see table). ANNs are attributed to Rosenblatt who, inspired by contemporary neuronal organizational biology, designed a perceptron that remains the basis for advanced networks today. ANNs are structured from interconnected processing elements (artificial neurons) in parallel, performing computational tasks (fig. 1). Before being fed to the neuron inputs are multiplied by a weight factor reflecting the excitatory or inhibitory strength of the connection from the input source to the neuron. The neuron then aggregates the multiple inputs using a simple summation operation. The sum of the weighted inputs plus a bias term goes through an activation function that behaves like a soft switch in determining whether the neuron will fire to send out an appropriate output signal. The commonest ANN used in medicine is the MLP, which comprises 3 neuronal layers. Between the first (input) and last (output) layers is a layer of interconnecting,

Previous diagnostic, staging and prognostic reports using AI in urological cancer

References	Technique	Tissue	% Sensitivity	% Specificity	% Accuracy	% Area Under ROC Curve
Diagnosis:						
Babaian et al[14]	ANN	Prostate	62	92		
Babaian et al[18]	ANN	Prostate	93	81		
Djavan et al[11]	ANN,* LR	Prostate	59–67, 33–60			88–91, 83–90
Pantazopoulos et al[34]	ANN	Bladder			91	
Parekattil et al[35]	ANN	Bladder	93	52	98	
Porter and Crawford[44]	ANN, LR	Prostate				74–76, 75–76
Qureshi et al[37]	ANN	Bladder			75–80	
Remzi et al[17]	ANN*, LR	Prostate	95	68, 8–54		83, 61–79
Spyridonos et al[32]	ANN	Bladder			95	
Tasoulis et al[33]	ANN	Bladder			90–97	
Staging:						
Batuello et al[21]	ANN	Prostate	44–64	81–82		77–81
Han et al[22]	ANN, LR	Prostate	21–59, 16–52	30–74, 27–59		77–88, 72–83
Mattfeldt et al[24]	ANN	Prostate			74–80	
Moul et al[38]	ANN	Testis	88	96	92	
Tewari et al[12]	ANN	Prostate	81–100	72–75		
Prognosis:						
Catto et al[8]	NFM,* ANN,* LR	Bladder	90–92, 90–94, 72–77	80–90, 89–96, 40–100	88–92, 90–95, 71–77	98, 91–98, 47–49
Catto et al[10]	NFM,† ANN,* LR	Bladder	88–100, 80–97, 38–65	99–100, 95–100, 61–80	94–100, 89–99, 47–74	99–100, 97–100, 47–87
Han et al[28]	ANN, LR	Prostate	16–45, 11–17			70–81, 68
Gulliford et al[27]	ANN	Prostate		55		
Ji et al[36]	ANN	Bladder			85	
Kattan[26]	ANN, Cox	Prostate			Median 67–69, 64–65	
Kattan[26]	ANN, Cox	Kidney			Median 71, 75	
Poulakis et al[29]	ANN,* LR	Prostate			84, 75	90, 79
					75	79
Tewari and Narayan[12]	ANN	Prostate	85	74	76	83
Naguib et al[14]	ANN	Prostate			60–80	

* Significantly better than LR.
† Significantly better than ANN.

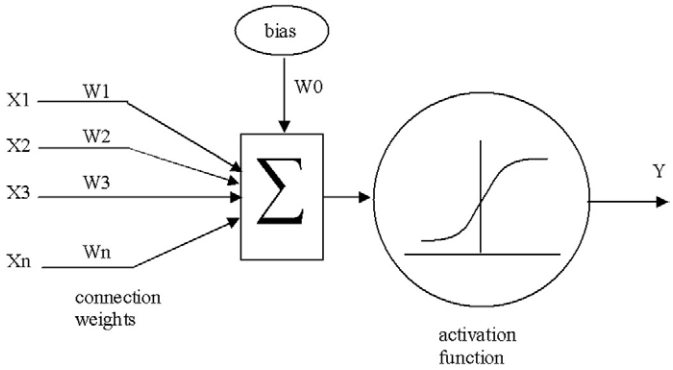

FIG. 1. Inner workings of single ANN neuron. For neurons in hidden or output layers inputs (*X1, X1,. . . , Xm*) come from outputs of neurons in previous layer. *W1, W2,. . .* , corresponding connection weights. *W0*, bias term added to total weighted sum of inputs to serve as threshold to shift neuron firing point. σ, sigmoidal activation serves as soft switch to produce large or small input (*Y*) depending on total weighted sum of inputs and bias term.

forward feeding neurons. This layer is hidden from the investigator and it is the analytical domain of the ANN. An MLP must have at least 1 layer of hidden neurons. The processing capacity or knowledge of an ANN is determined largely by the type, number and arrangement of neurons in the network, and it is defined by the connection weight values between neurons. Such knowledge is acquired through a learning phase, during which data are repeatedly fed through the ANN to adjust connection weights and satisfy predetermined performance goals.

NFMs

An NFM is a fuzzy inference system embedded in an ANN that has the benefit of using available ANN training methods to find the parameters of a fuzzy system. Thus, NFMs appear similar in design to ANN with input, analytical and output layers. Because the analytical layer uses a fuzzy logic rule base, it enables the NFM to be transparent because it can be de-fuzzified (fig. 2). Its simplicity decreases the overtraining seen with ANN. Transparency allows the most influential input variables to be identified and clinically validated.[8] The optimal number of fuzzy rules can be determined separately via the fuzzy c-means clustering algorithm with modified fuzzy entropy as the criterion of cluster validation.[9,10] The simpler, transparent nature of NFMs makes them more favorable to use than ANNs since they are open to scientific rigor and can produce more accurate modeling.[10] The strength of neuro-fuzzy systems involves 2 contradictory requirements in fuzzy modeling, that is interpretability vs accuracy. In practice 1 of the 2 properties prevails. The neuro-fuzzy in fuzzy modeling research field is divided into 2 areas, including linguistic fuzzy modeling, which focuses on interpretability, mainly the Mamdani model, and precise fuzzy modeling, which focuses on accuracy, mainly the Takagi-Sugeno-Kang model. Regarding clinical application, NFM can perform tasks similar to ANN (see table).

AI in Urological Cancer

The potential of modeling clinical data sets to reveal insights into disease behavior has led many investigators to develop models using machine learning and statistical methods (see table). For the clinician AI has been used to optimize cancer diagnosis,[11] staging[12] and prognostic prediction,[13] while for the researcher AI has been used to determine novel biomarkers[8,14,15] and perform data mining on large data sets, such as those generated by gene expression arrays.[16]

CaP Diagnosis and Staging

The clinical need to diagnose and accurately stage CaP combined with the large homogenous data sets available and numerous objective descriptive variables has led many groups to explore AI within these roles. In general most investigators have used ANN and they reported this improve diagnostic accuracy over nonAI methods (see table).

For diagnosis Babaian et al found that an ANN decreased the need for prostate biopsy by 50% compared to using only serum PSA.[14] Djavan et al developed 2 ANNs to diagnose CaP at low PSA (2.5 to 4.0 and 4 to 10 ng/ml).[11] Each was superior to conventional parameters and could be used to aid in urological referral. Remzi et al found that an ANN outperformed LR for predicting CaP in repeat prostate biopsy using PSA isoforms.[17] One of the best studied diagnostic ANNs is the ProstAsure index, an ANN derived algorithm using multiple serum tumor markers that produces a single valued diagnostic index.[18] This index was validated through clinical studies, outperforms free PSA and has become one of the first commercially available ANNs.

Bayesian and fuzzy systems have also been used for diagnosis. For example, Saritas et al used PSA, patient age and prostate volume as input parameters to determine the need for biopsy and the risk of cancer based on fuzzy expert system.[19] Montironi et al developed several Bayesian networks that improved the pathological description of prostate tissues.[20]

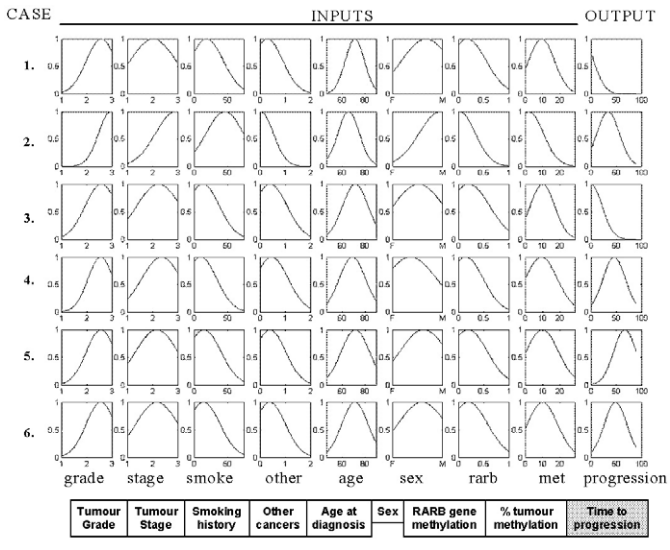

FIG. 2. NFM output and linguistic translation. Fuzzy format shows graphic representation based on so-called membership functions. For each variable quantitative points are joined in qualitative manner using fuzzy logic. Result is curve. When summed in series and interpreted, output is produced, which in this case is time to tumor progression in months. Whole model comprises series of rules that must be used together in parallel to generate output. Below, table shows linguistic translations for rules 1, 3 and 6.

For staging several ANNs that were developed using conventional preoperative data have been reported. For example, Tewari et al used 1,200 patients to develop an ANN with high sensitivity and specificity for various pathological parameters, such as node, seminal vesicle and margin status.[12] Batuello et al reported a larger ANN study in 6,454 patients that had similar high predictive accuracy for nodal spread.[21] A direct comparison of a staging ANN and the Partin nomogram was made by Han et al, who found that ANNs were slightly better for predicting organ confinement and nodal spread (see table).[22] Horner et al developed a Bayesian network based on the Partin tables to model CaP pathology from the single bin Gleason score.[23] They observed that staging accuracy could be improved if additional independent data were available. Studies of novel biomarkers, such as comparative genomic hybridization[24] and proteomic diagnostic classification using decision trees and MLP neural networks,[25] have been reported but they were not sufficiently robust to support their routine introduction.

CaP Prognosis

For prognostic prediction AI techniques have characteristics that make them potentially more favorable than statistical regression. These characteristics include the ability to model nonlinear relationships in the presence of contaminating data, construct symbolic and interpretable systems, and allow individual patient predictions. However, all methods struggle with predictions when handling censored data. Several groups have reported large studies using ANNs to predict CaP recurrence following surgery and radiotherapy.[26,27] Tewari et al developed an ANN using conventional parameters in 1,400 patients with radical prostatectomy, which accurately (76%) identified those with PSA progression.[13] Han et al compared LR and ANN to examine the role of Gleason 4 + 3 vs 3 + 4 for predicting PSA progression.[28] They found that ANN was slightly superior. In addition to clinicopathological details, various groups have modeled the effect of extra information on predicting CaP behavior. For example, Naguib et al developed an ANN using experimental factors (p53 and bcl-2 expression) to predict recurrence and treatment response with 60% to 80% accuracy.[15] Poulakis et al improved the predictive accuracy of ANNs compared to that of LR and nomograms by adding pelvic coil magnetic resonance imaging to PSA and tumor grade.[29]

While most investigators have found that the application of AI improves outcome prediction accuracy (see table), Kattan analyzed 3 large urological data sets and found that ANNs had an accuracy similar to that of Cox regression.[26] For CaP recurrence the median accuracy of ANN was 69% for external beam radiotherapy and 64% for brachytherapy vs a median Cox regression accuracy of 67% and 65%, respectively. This finding supports the conclusions of other groups suggesting that suggest AI models are often flawed by over fitting and underestimating misclassification.[1,3]

Bladder Cancer Diagnosis and Grading

UC behavior is strongly associated with tumor grade, which is a semisubjective pathological parameter. To decrease the interobserver variation of this measure researchers have used AI. Various designs have been used successfully, including a Bayesian belief network,[30] fuzzy logic system,[31] support vector machine and probabilistic neural network.[32,33] The last 2 reports combined the ANN with an image capture system to fully automate tumor grading. When tested, this automated system achieved a grading accuracy of 90%, 94.9% and 97.3% for grades I to III tumors, respectively.[33] When the diagnosis was unknown, a back propagation ANN correctly classified 100% of patients with benign and 94.51% with malignant bladder disease.[34] Parekattil et al found that the addition of nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to hematuria and cytology improved the accuracy of a diagnostic ANN for UC.[35] It would decrease the cost reductions of almost 50% in the United States for diagnosis and new UC cases.

Bladder Cancer Prognosis

Several groups have used AI to predict UC behavior and interrogate potential prognostic variables. Ji et al used a hybrid neuro-fuzzy classifier to determine the influence of bilharzia on the long-term outcome of patients with infection and UC.[36] They compared their fuzzy model with LR and ANN by analyzing a benchmark data set, that is Wisconsin breast cancer data. The hybrid neuro-fuzzy classifier was highly efficient with an accurate classification rate of 97.1% for Wisconsin data and 84.9% for UC data, and it suggested that bilharzia is important for UC prognosis. Catto et al modeled a series of UC using experimental and clinical parameters with ANN, NFM and LR.[8] They found that the 2 AI methods were more accurate than LR and observed the transparences benefit of NFM over the ANN. This transparency allows the model to be understood and facilitates individual variable interrogation (fig. 2). In a subsequent report they used a larger input panel and found that NFM was more accurate than ANN and LR.[10] Interrogation of 11 prognostic variables suggested that only tumor grade, stage, smoking history and p53 status were needed to accurately predict disease behavior. Qureshi et al compared the predictive accuracy of an ANN with that of experienced clinicians.[37] They found that the ANN was better for muscle invasive disease (mortality accuracy 65% vs 82%) but similar to clinicians for predicting superficial cancer behavior (recurrence accuracy 75% vs 79%).

Testicular and Renal Cancer

Few investigators have used AI to analyze testis or renal cancer. Exceptions include a comparison of a custom designed and a commercial ANN to stage testicular cancer using pathological parameters.[38] The custom ANN performed better than the commercial ANN (92% vs 80% accuracy), highlighting the need for individualized network refinement by the researcher, which currently prevents the widespread commercial introduction of these methods. With regard to renal cancer Kattan used ANNs and Cox regression to predict behavior (median accuracy 71% for ANN and 75% for Cox),[26] supporting the comment.

Urological Imaging

The operator dependency inherent in radiological techniques, notably ultrasound, has led investigators to develop scanning machines with automated image interpretation analogous to those in histopathology for diagnosis and radiotherapy planning.[39] AI provides a useful analytical method for linking automated image analysis with diagno-

sis. Maclin et al trained an ANN to correctly interpret renal ultrasound images with 99% accuracy in 52 cases,[40] and Prater and Richard used an ANN to identify prostatic pixels on an ultrasound image with 87% accuracy.[41] To improve ultrasound features several groups have used radio frequency to gain more information from prostatic tissue. Scheipers et al developed an adaptive neuro-fuzzy inference system to compare automated tumor diagnosis using spectral (radio frequency) and conventional (ultrasound) imaging parameters.[42] The adaptive neuro-fuzzy inference system outputs were validated using 100 radical prostatectomy specimens and the radio frequency data were found to improve automated performance (area under the ROC curve 84% to 86% vs 70% to 74%). Feleppa et al combined radio frequency with PSA using ANNs to define tissue-type imaging.[43] Other investigators have used clinical and radiological parameters to predict the need for and outcome of prostate biopsies using ANNs,[44] for example expert systems,[45] fuzzy logic,[46] neuro-fuzzy systems[47] and conventional classifier.[48]

Planning Treatment

The optimal delivery of radiotherapy to a tumor is difficult due to delivery (beam ballistics, collimator settings and wedge angles), targeting (tumor and adjacent viscera) and patient (size and shape) variables. If variations in patient habitus were adequately sampled, AI could be used to automatically map a tumor and plan treatment. An expert systems approach to standardized treatment planning was developed for CaP that led to improved planning efficiency and a decrease in treatment iterations for the optimized dose.[49] Meyer et al developed a Bayesian network to aid in the selection of intensity modulated radiotherapy planning for CaP.[50] The network used clinicopathological variables in addition to dosimetry, complications and survival statistics from clinical trials, and it ranked each radiotherapy map using an influence diagram. These maps demonstrated that this model could successfully replicate planning strategies while incorporating trial data.

CONCLUSIONS

AI has been used in clinical decision making since the early days of computing but it is only recently that DSSs have been introduced to clinical practice. It is likely that the accuracy and role of AI will increase with the discovery of novel biomarkers and the use of electronic medical records. AI has the flexibility and learning capability necessary to assist physicians in their decision making. When correctly used, AI models can be superior to standard statistical methods and allow more thorough and flexible interrogation of data with reliable prediction of disease outcomes. Most current AI models are limited by the requirement for operator refinement, preventing widespread commercial uptake, although some are cited in this survey. Understanding the basis of AI methods and their potential, including the transparency of specific systems such as fuzzy logic, will allow these exciting techniques to be developed further and form an important part of the physician armamentarium for treating patients with cancer.

APPENDIX

Different AI Methodologies

Method	Application	Advantages	Disadvantages
Bayesian network	DSS	Combines expert knowledge with data	Can only model linear dependencies
Expert systems	Diagnosis DSS Treatment planning	Can provide consistent answers Hold significant level of information Combine multiple human expert knowledge Review transaction that humans may overlook	Lacks flexibility to adapt to changing environment Does not have creativity when unusual circumstances occur Cannot explain answer and logic behind it
ANN	Modeling Prediction Classification Image processing	Can model high dimension problems Can model nonlinearity	Needs lot of data Nontransparent Training depends on cost function
NFM	Modeling Prediction Classification	Needs few data Transparent Can model nonlinearity	Cannot support high dimension problems
LR	Modeling Prediction	Simple to implement	Generates linear models only

Abbreviations and Acronyms

AI = artificial intelligence
ANFIS = adaptive neuro-fuzzy inference system
ANN = artificial neural network
CaP = prostatic carcinoma
DSS = decision support system
LR = logistic regression
MLP = multilayer perceptron
NFM = neuro-fuzzy logic modeling system
PSA = prostate specific antigen
UC = urothelial cancer

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