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## Toward Personalized Guidelines in Bladder Cancer

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Guidelines, by their nature, seek to outline the generalized approach to treating a group of patients who have a particular ailment. In the case of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), the focus is on the many aspects of cancer care across a spectrum of malignancies. In seeking a generalized approach, most treatment guidelines will attempt to synthesize the existent literature and scientific evidence to offer the most rational and reasonable alternatives for treating a given condition. The range of theoretical options is vast, so virtually all guidelines will attempt to risk-stratify patients into various strata or groups and then tailor the therapy to that risk group. This is a time-honored approach that has served the medical community well for many decades.

However, the fundamental parameters used to assign risk are remarkably crude. In most conditions, risk assignment is fundamentally driven by tumor histology, stage (typically using the TNM classification), and some measure of grade or differentiation. The tools available to measure, for example, T stage have advanced considerably and now include a wide variety of imaging technologies. Similarly, in some tumor types, biomarkers can add significant prognostic value when performing risk stratification for patients. In genitourinary cancers, the best examples would be serum prostate-specific antigen in prostate cancer and the testis tumor markers  $\alpha$ -fetoprotein and  $\beta$ -HCG.

In many respects, though, the relative principles by which we risk-stratify patients has not fundamentally changed. The histology and grade assigned by the pathologist and the TNM stage based on imaging are the mainstays by which we determine risk. As a consequence, all the algorithms to date still treat an individual patient the same as all other patients within a particular larger group. In so doing, algorithms often recommend therapies that may or may not be effective.

The alternative to such a "lumping" approach is what many would now term "personalized" medicine. The advent of cheaper, faster, and higher-fidelity methods to assess DNA mutations, gene expression, DNA methylation, and protein expression has generated an unprecedented volume of in-depth data on individual patients and their cancer. For the first time, there is hope that the ability to comprehensively characterize a particular cancer will allow clinicians to offer a truly personalized or tailored approach.

In genitourinary cancers, one of the best examples of this promise is in bladder cancer. Within the past 4 years, at least 4 different groups have independently tested the expression profile of locally advanced bladder cancers (typically those undergoing radical cystectomy) and assigned a molecular subtype based on the gene expression profile of the tumors.<sup>1-4</sup> What is particularly noteworthy is the remarkable overlap in the subtyping across these independent studies, despite the fact that the methodology across these efforts differed. In effect, these studies were able to validate each other's findings. In many ways, they have reshaped the entire framework by which we view the molecular drivers of urothelial carcinoma.

Furthermore, although this work is not ready for clinical use yet, the molecular subtyping framework may be able to predict response to systemic therapy or survival after local therapy. Although not realized yet, the promise is that in the not too distant future, a patient's bladder tumor will be analyzed not only by a pathologist but also by high-throughput molecular profiling that will be able to subtype the cancer and predict how it will respond to different treatment approaches. Thus, an individual patient could be assigned a tailored therapeutic strategy based on the molecular profile of the tumor.

One fascinating potential repercussion from such an advance is in the role of cancer treatment guidelines in the face of a fully mature personalized medicine framework. Theoretically, if personalized medicine reaches its full potential, a patient's treatment course will be fully outlined based on a molecular signature algorithm rather than a guideline in the traditional sense. On reflection, the concept is quite profound in its scope. At some point in the future, it might be possible that a biopsy of the tumor will determine exactly what treatment the patient will receive. This may be nuanced by additional information, such as the traditional TNM stage, grade, or other factors, but the fundamental driver of a patient's treatment will be a molecular signature individualized to that particular tumor. Theoretically, much of the "art of medicine" may be subverted to the proscriptive results of a laboratory test. This is probably far-fetched, but it is the logical extension of personalized medicine's real promise: the ability to take the guess work, or art, out of deciding on a particular treatment regimen for a patient.

The promise of personalized medicine has captured the imagination of patients and caregivers alike, but significant barriers must still be navigated before its full potential is realized. In bladder cancer, the first hurdle is how to translate insights on the molecular drivers of disease progression and disease subtyping into individualized targeted therapeutics. One challenge is that many of the oncogenic and tumor suppressive pathways that are disrupted are not currently targetable. Knowing what pathway has been altered is not enough. To truly take the next step in therapy, that pathway must be targeted such that the appropriate balance is restored.

The ability to screen and test small molecules that can target a wide range of biologic molecules on a large scale is improving steadily. There is a wider and wider range of signaling pathways for which targeted molecules are now approved for use or are being tested in early-phase clinical trials. Nevertheless, most biologically relevant pathways still cannot be directly targeted for therapy. It will be some time before we have the capacity to target the hundreds of molecules that may prove important in the biology of urothelial carcinoma.

The second major challenge is how to prove that a given genetic signature indicates that a specific treatment regimen should be used. For some tumors, perhaps most notably breast cancer, the tumor marker characteristics can tailor therapy to a much larger degree than previously possible. However, in the case of bladder cancer, our progress is crude at best. Further progress will require large-scale prospective trials with tumor sampling at treatment start, molecular subtyping, and defined treatment regimens with ongoing response monitoring. Truly working out all the specific combinations of molecular signatures with treatment regimens will take years and be further complicated by the need to resample the tumor at relapse to determine the mechanisms of resistance and define the next treatment course.

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A third challenge, and perhaps the one that may pose the biggest potential hazard, is the increasing appreciation of tumor heterogeneity. Ground-breaking work in renal cell carcinoma has shown significant differences in the molecular profile of the primary tumor and metastatic foci within the same patient.<sup>5</sup> Indeed, even within the primary tumor, the molecular profile changes from region to region. The same phenomenon is also beginning to be appreciated in urothelial carcinomas. In fact, pathologists have observed this phenomenon histologically in bladder cancer specimens for years. Many invasive tumors will have areas with squamous or glandular differentiation within them. These are often scattered foci and therefore the tumors are still called *urothelial carcinoma*. If the foci are large enough or constitute a significant portion of the tumor then perhaps the term *with squamous differentiation* may be added, but they are still treated as urothelial carcinoma.

However, it stands to reason that if the histologic appearance differs markedly from region to region, then the molecular signature is likely to vary across these regions as well. This heterogeneity raises a fundamental problem for personalized medicine. It implies that to know the full genetic profile of a particular patient's cancer, one must have extensively sampled both the primary tumor and all the available metastatic sites. From a practical standpoint, this is not really feasible, at least for the metastatic sites. Even if it becomes possible to do such extensive sampling, this then poses a new problem. It will be challenging enough to try and match a single molecular signature with a treatment regimen. If a clinician/scientist now has multiple signatures for each patient's cancer, how do we decide which of these is the one to use to define the patient's treatment regimen? We may find that, even with many potential branching networks a tumor may take, some fundamental mutations/alterations lie at the very roots and drive all that come after. If that is the case, then heterogeneity becomes less of a problem. As a research community, however, we still have a long way to go in defining those fundamental alterations and which of them will be targetable.

The challenges are clearly large and will take some time to overcome. As a surgeon-scientist, I remain confident that, given sufficient time and effort, we will develop the ability to personalize medicine based on the molecular profile of a patient and his or her particular cancer. However, I am also sure this will take a considerable amount of time and is unlikely to be fully possible in the near term. The promise is worth pursuing, but in the meantime, the "art of medicine" and the need for clinical guidelines as a decision aid for physicians and their patients remain very much alive.

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