# 58. Prostate


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## Emerging Prognostic Factors for Clinical Care

### Molecular and Genomic Assays

Biopsy information, such as the proportion of biopsy regions (i.e., cores) or biopsy tissue positive, is an indicator of disease burden that complements DRE findings and may further subclassify clinically localized disease.[1,2] However, the reporting of biopsy information is not standardized, and there is variation in collecting, processing, and describing specimens in terms of "core" or tissue involvement with carcinoma. As a consequence, the integration of biopsy information into prognostic classification systems has been widely accepted and the added value is not clear.[3]

For men with metastasis, the site of disease may be prognostic. In a large meta-analysis, survival differed based on the site of metastatic disease for men with metastatic castrate-resistant prostate cancer. Men with lung and liver metastases appear to fare worse than men with bone and nonvisceral involvement.[4]

## Risk Assessment Models

Prognostic models will continue to play an important role in 21st century medicine for several reasons.[5] First, by identifying which factors predict outcomes, clinicians gain insight into the biology and natural history of the disease. Second, treatment strategies may be optimized based on the outcome risks of the individual patient. Third, because of the heterogeneity of disease in most cancers, prognostic models will play a critical role in the design, conduct, and analysis of clinical trials in oncology.[5] If developed and validated appropriately, these models may become part of routine patient care and decision-making in trial design and conduct.

The AJCC Precision Medicine Core (PMC) developed and published criteria for critical evaluation of prognostic tool quality,[6] which are presented and discussed in Chapter 4. Although developed independently by the PMC, the AJCC quality criteria correspond fully with the recently developed Cochrane CHARMS tool for critical appraisal in systematic reviews of prediction modeling studies.[7]

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Existing prognostic models for prostate cancer meeting all of the AJCC inclusion/exclusion criteria and meriting AJCC endorsement are presented in this section. A full list of the evaluated models and their adherence to the quality criteria is available on www.cancerstaging.org.

The PMC performed a systematic search of published literature for prognostic models/tools in prostate cancer from January 2011 to December 2015. The search strategy is provided in Chapter 4. The PMC defined "prognostic model" as a multivariable model where factors predict a clinical outcome that will occur in the future. Each tool identified was compared against the quality criteria developed by the PMC as guidelines for AJCC commendation for prognostication models (see Chapter 4).

Fifteen prognostication tools[8-22] for prostate cancer were identified: seven for patients with localized disease,[8-15] one for non-castrate patients with metastatic cancer,[16] and six for patients with metastatic castration-resistant prostate cancer.[17-22]

Of the 15 available models, 13 models were rejected based on the predefined criteria for exclusion.[8-16,18,19,21-23] For most of the models, the proportion of patients with missing data in the validation set was not stated.[8-14,16,19,23] Three of the models did not report on the follow-up status of the patients.[11,19,22]

One of the models for patients with localized disease met 11 out of the 14 criteria, although the endpoint was based on prostate cancer-specific survival rather than overall survival.[8] For this model, the equation was not readily available, and the number of events was unspecified.[8] Several models for patients with localized disease did not use overall survival as the outcome,[8-15] or were not validated (internally or externally), or did not provide the calibration plots. Hence, the PMC determined that these models were not readily available for use.[8-15] The model for non-castrate patients with metastatic disease lacked sufficient details on the number of events and on calibration, and was neither validated nor readily available for use.[16]

Among the six models for metastatic disease, two met all inclusion criteria[20,24] and are available online (Table 58.1). One model was for chemotherapy naïve patients,[24] and the other model was for patients for whom first-line chemotherapy had failed.[20] Other models in the advanced metastatic setting met a subset of the inclusion criteria but did not include a calibration plot or were not readily available for use.[18,21-23] The sixth model was presented in a scientific meeting but has not been published at the time of this writing.[21] Nevertheless, a separate publication reported the results of the validation of this model.[19]

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Fifteen prognostic models in prostate cancer were identified, but only two models for metastatic disease met all predefined AJCC inclusion and exclusion criteria and are, therefore, endorsed by the AJCC.[20,24] Both of the endorsed models were based on data from large phase III trials in metastatic patients and were externally validated.[20,24] In the models for patients with localized prostate cancer disease, an outcome other than overall survival was used.[8-15] Although another endpoint may be appropriate in this setting, the present AJCC guidelines[6] focus on the use of overall survival as the outcome of interest. It is expected that these guidelines will evolve over time and that other endpoints besides overall survival will be developed for patients with localized disease.

Recent guidelines on the reporting of prediction model development and validation have been published.[25,26] It is important to emphasize that validation will always be a fundamental step in prediction modeling.[27] Although external validation is considered ideal, model developers may not have access to external data.[5] Other validation approaches, such as bootstrapping, may be acceptable.[27,28] Two key missing criteria that were lacking in the majority of models identified in the AJCC review process were calibration plots and the tools to facilitate clinical utility. These should be, and are, easily addressable. In following these guidelines, authors will enhance the rigorous development, validation, and overall quality of future prognostic tools, resulting in a larger number of tools being endorsed by the AJCC.

**TABLE 58.1.** Prognostic tools for prostate cancer that met all AJCC quality criteria.

| ***Approved Prognostic Tool*** | ***Web Address*** | ***Factors Included in the Model*** |
|---|---|---|
| Metastatic castration-resistant prostate cancer[24] | https://www.cancer.duke.edu/Nomogram/firstlinechemotherapy.html | ECOG performance status, site of metastases, PSA, hemoglobin, albumin, alkaline phosphatase, LDH > 1 ULN, opioid analgesic use |
| Metastatic castration-resistant prostate cancer treated with second-line chemotherapy[20] | https://www.cancer.duke.edu/Nomogram/secondlinechemotherapy.html | ECOG performance status, visceral disease, progression on docetaxel, duration on hormone, measurable disease, pain, PSA, hemoglobin, alkaline phosphatase |

## Recommendations for Clinical Trial Stratification

The following variables should be considered for stratification in future clinical trials for prostate cancer:

**Primary tumor**

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T Category
Serum PSA
Grade Group with or without Gleason score
Number and percentage of positive biopsy regions (i.e., biopsy "cores")

**Regional lymph nodes/distant metastases**
Clinical Factors

- Performance status
- M0 versus M1 category

Pathological Factors

- Extranodal extension of cancer
- M1b (bone) versus M1c (lung, liver, brain, with or without bone)[4]

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