



The AJCC Gets Personal: Calculating Individualized Prognosis for Cancer Patients

Carolyn Compton, MD, PhD

Chair, Scientific Advisory Committee, Indivumed GmbH

Professor of Life Sciences, ASU

Professor of Laboratory Medicine and Pathology, Mayo Clinic

Adjunct Professor of Pathology, Johns Hopkins

Adjunct Professor of Pathology, University of Arizona

CMO, National Biomarker Development Alliance

CMO, Complex adaptive Systems Institute

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Prognosis: Predicting Future Outcomes

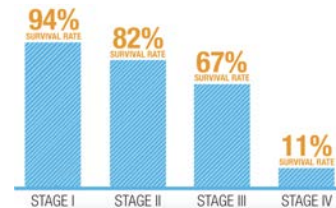
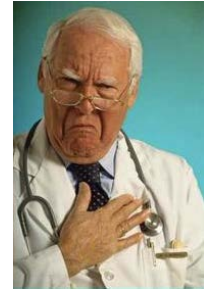


Prediction is very difficult, especially if it's about the future.

(Niels Bohr)

The Evolution of Modern Prognostication

- An opinion, based on medical experience, of the likely course of a medical condition
 - The patient is likely to die from their disease
- An estimate, based on outcomes data from of similarly classified (staged) patients, of the likely course of a medical condition
 - The patient's tumor is stage II, and 20% of patients with stage II disease range die from their disease
 - The patient is classified ("binned") within a "risk group" of similarly classified patients
- A calculation, based on multiple objectively measurable features know to influence outcome, of the specific risk for an individual patient of dying of their disease (personalized prognosis)
 - The computational integration of the patient's validated prognostic factors indicate that the probability of death for this patient is 17%



What Is Prognosis?



- Predicting the *future* after diagnosis and primary treatment
 - Risk of dying of the disease
 - Likelihood of surviving the disease
 - Usually expressed in terms of percent “chance” of 5-yr survival (overall survival)
 - Other: disease-free survival, cancer-specific survival
- Differs from “diagnosis” which is determining a *present* fact
- “An expert prediction of outcome is based on an accurate diagnosis, knowledge of the natural history of the disease, the disease’s response to treatment, and *the progression of the disease in the patient in question*”
 - Bailey, Concise Dictionary of Medical-Legal Terms

Prognostication in Oncology: Why?



- **Patients need to know**
 - How bad is it? What are my chances? How long do I have?
 - Will the treatment cure me?
 - For me, is it worth going through treatment?
- **Physicians need to know**
 - Appropriate patient management: the right treatment for the individual patient
 - Avoid over- or under-treatment
- **Scientists need to know**
 - Are “like” patients being compared?
 - Is therapy altering outcome?
 - Are we making progress against cancer (are outcomes changing)?

How Is Prognosis Estimated Most Commonly?

Medical prediction is typically based on statistical averages from **population data** relating to **all** patients who have comparable disease features



- For any **given** patient, the prediction is most often imprecise
- Example: For stage II colon cancer, complete surgical excision is curative for 80% of patients; an individual patient wants to know if they are one of the 80% or not!
- For *individualized* patient prognosis, computational algorithms that integrate multiple factors specific to a given patient's case are needed
- We are not there yet, but that is where we are going

What Determines Prognosis?

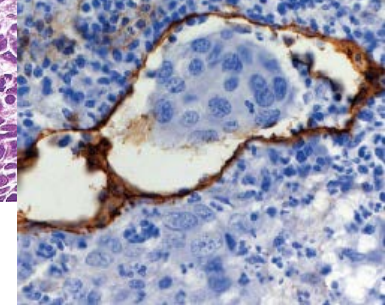
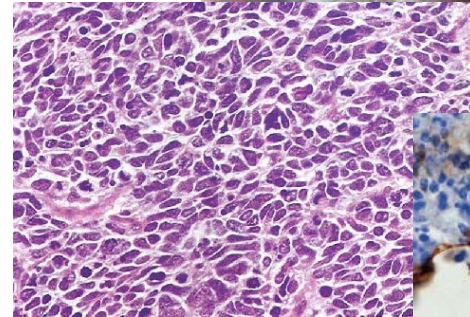
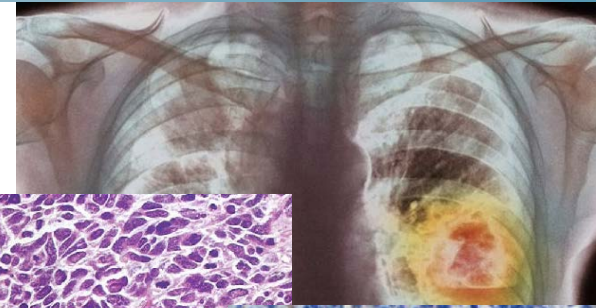
PROGNOSIS

- Influenced by a multitude of factors
 - “Prognostic factors”
 - Factors may increase (favorable or positive factors) or decrease (negative or adverse factors) the likelihood of survival
- Prognostic factor types
 - Those related to the **tumor***
 - Those related to the **patient***
 - Those related to the medical **environment**

*** Related to the need for more validated biomarkers!**

Tumor-related Prognostic Factors

- Tumor type or subtype
- Tumor grade
- Tumor stage (a dominant factor)
- Presence of specific invasion patterns:
 - Venous invasion
 - Lymphatic invasion
 - Peri-neural invasion
- Where the tumor is located (anatomic location and adjacencies)
- Specific pathological or molecular features
 - Presence of abnormal chromosomes
 - Presence of mutations or mutated proteins or the over-expression of normal oncogenic proteins
 - HER2 over-expression in breast cancer is an adverse prognostic factor but a favorable “predictive” factor for response to Herceptin [targeted] therapy)



Molecular Testing For Cancers

Done for 3 main reasons:

- Diagnosis: certain molecular features may be an integral part of the diagnosis/diagnostic category of the tumor
- Prognosis: certain molecular features may be associated with a better or worse outcome (for the same diagnostic type of tumor)
- Prediction of response to therapy: certain molecular features are biologically related to and predict response or non-response to specific therapies
 - “Companion diagnostics” refer to tests for molecular features that are targets for specific molecularly targeted therapies:

Molecular Testing For Cancer



Diagnosis

- The majority of the lymphoid neoplasms require 1 or more molecular tests, such as immunophenotyping, molecular studies, and/or cytogenetics, to determine the correct diagnosis
- Follicular lymphoma example: gene/protein panel [- sIg+ (usually IGM +/- IGD, IGG, IGA), PanB+, CD10+/-, CD5-/+ , CD23-/+ , CD43-, CD11c-, CD25-; overexpression of BCL2+, BCL6+; IGH and IGL gene rearrangements, t(14;18)(q32;q21) with rearranged BCL2 gene]

Prognosis

- Breast cancer example: MammaPrint® multigene expression test to predict likelihood of recurrence in 10 years

Prediction (of response to therapy)

- Breast cancer example: Herceptest for over-expression of HER2 is Herceptin therapy gateway
- Colon cancer example: RAS mutation precludes use of anti-EGFR therapies

Patient-related Prognostic Factors

- Patient's age
- Patient's gender
- Patient's overall condition ("performance score")
- Presence of other medical conditions ("co-morbidities")
- Function of vital organs
- Presence of cancer-specific symptoms:
 - Weight loss
 - Pain
 - Fever



Environment-related Prognostic Factors

- The socioeconomic conditions and healthcare policies of the region (country, state, etc.)
- The availability of oncology care in local region
- The track record of the treatment institution for the specific disease (outcomes for patients compared to comparable patients nationwide)
- The patient volume in the institution
- The degree of experience of the surgeon
- The degree of experience of the management “team”
- The use of a standard of care treatment plan
- The validity and performance status of the diagnostic tests



The AJCC and the Precision Medicine Core

AJCC Goals:

- Prepare for a future that includes personalized medicine
- Build on the success of TNM
- Shape the implementation of precision medicine through the 8th Edition

Precision Medicine Core group charged with how to use information *beyond* stage to:

- Increase prognostic accuracy
- Help guide patient management and classification



AJCC
American Joint Committee on Cancer

AJCC: Going Beyond Stage as a Patient Classifier

- **Classifier**
 - Divides patients into ordered risk strata
 - Cut-points for “bins” are based on probability estimates
 - Stage is an example: stages I-IV are bins correlating with increasingly poor prognosis
 - Limiting factors:
 - Number of parameters that can be manageably included
 - Inherent heterogeneity of patients within a given bin
- **Calculator**
 - Computational integration of factors to deliver a more precise estimate of outcome for an individual patient with probability estimates
 - No inherent limit to numbers of factors that can be included

The AJCC Surveys the Landscape of Prognostication Tools

- The Precision Medicine Core built on previous work of the AJCC Molecular Modeller's Working Group, formed in 2008, that identified and reviewed 176 prognostication calculation tools for melanoma, colorectum, lung, breast and prostate cancers
- Many deficiencies and inconsistencies were noted
- Wide variation in:
 - Degree of evidence supporting each tool
 - Mode of presentation / calculation
 - Inclusion of appropriate internal and external validation
 - Selection of prognostic factors
 - Target population
 - Outcome measure chosen



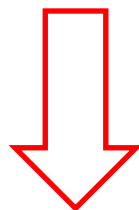
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Prognostication Tools and Opportunities for AJCC

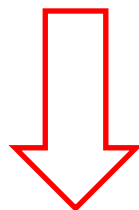
- Play an important role in improving the quality of prognostication tools
- Provide a centralized resource for assessment of prognostication tools
 - To provide a service to cancer care providers and patients
 - To reduce duplication of effort and reveal gaps
- Create a central data repository with dedicated expert support
 - To allow for the development of new tools
 - To update existing high quality tools
 - To conduct external validation of promising tools
- Help to meet the need for assessment of the *impact* of prognostication tools on practice and outcomes
 - See: Ann Intern Med 2006;144:201-209

The AJCC Defines a Path Forward

1) Develop a list of criteria to assess validity



2) Critically appraise all identified prognostication tools



3) Create a resource of approved, AJCC-endorsed prognostication tools for the cancer community

Develop a List Of Criteria to Assess Validity

- Two-day PMC meeting in Phoenix, AZ in January 2015
- PMC members:
 - **Biostatisticians**
 - **Prediction Tool Developers**
 - **Data scientists**
 - **Epidemiologists**
 - **Disease experts**
- Define set of Inclusion and Exclusion criteria for AJCC endorsement
- 13 inclusion criteria and 3 exclusion criteria were defined
- Emphasis placed on:
 - **Performance metrics of the tool**
 - **Implementation clarity**
 - **Clinical relevance**
- Endorsement criteria were published: Kattan MW et al., CA: a cancer journal for clinicians. January 19, 2016

AJCC Endorsement Criteria

Inclusion:

- Overall or disease-specific survival must be the outcome predicted
- A clinically relevant question must be addressed
- The relevant predictors or a justification for omitting a relevant predictor must be included
- Included patients must be well described along with the inclusion/exclusion criteria for them
- State of the art internal validation or truly external validation must be performed
- Time zero must be well defined
- All predictors must be known at time zero and defined well enough for someone else to use
- Sufficient detail must be available to implement the model
- A measure of discrimination must have been reported.
- Calibration in the small must be assessed (from the external validation data set) and provided.
- The model developed in a time frame and practice setting c/w contemporary patients with disease.
- All initial treatment(s), if any, must be clearly delineated, as well as frequency/timing.
- Development and/or validation of the model must appear as a peer-reviewed journal article.

Exclusion:

- A substantial proportion of patients had essentially no follow up.
- No information on number of missing values in validation dataset.
- The number of events in the validation dataset is small.

AJCC-Endorsed Prognostication Tools

The number of tools identified and evaluated by the PMC:

- 27 for breast cancer
- 37 for colorectal cancer
- 16 for prostate cancer
- 27 for lung cancer
- 7 for melanoma
- 4 for head and neck cancer
- 4 for soft tissue sarcoma
- 19 for selected hematologic malignancies

The number that were endorsed:

- 2 for colon
- 4 for head and neck
- 2 for prostate
- 2 for breast
- 1 for soft tissue sarcoma (GIST)
- 0 for melanoma
- 0 for lung

Create a Resource of Approved, AJCC-endorsed Prognostication Tools

- The work of the PMC has just begun
- Aim to evaluate all tools for adult cancers included in the 8th Edition
- Make newly evaluated tools known through the AJCC website
- Identify gaps in prognostication tool landscape
- Encourage tool building for the cancer community using AJCC criteria
- Possibly build new AJCC tools *de novo* from high-quality data sets using AJCC criteria from the outset

Vision

- Prognostication is made personal
- AJCC takes a bold step forward to lead
- Quality, consistency, availability, utility drive the endorsement of AJCC
- The first step in bridging the worlds of patient classification (stage groups) and individualized prognostication (individualized risk score)
- The vision of precision medicine is enabled





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A Short History of Prognostication



- Mantic prognosis, the foretelling of the outcome of an illness based on omens and magic
 - An ancient practice that can be traced back to the beginning of recorded history
- Semiotic prognosis, the foretelling of the outcome of an illness based on clinical findings
 - Traced back to Sumerian civilization of 2000 BC
 - Peak sophistication with Hippocrates about 400 BC
 - Relied on complexes of symptoms and signs that predicted a good or bad outcome
 - Resembled modern medicine: clinical observation applied by pattern recognition

