DEALING WITH COMPETING MORTALITY IN CANCER PATIENTS: ENHANCING THEN TNM STAGING SYSTEM THROUGH INCLUSION OF COMORBIDITY COPYRIGHT NOTICE

Dealing with Competing Mortality in Cancer Patients:Enhancing the TNM Staging System through Inclusion of Comorbidity

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Introduction

- TNM -- A cornerstone of cancer staging for more than 30 years
- “To develop systems for the clinical classification of cancer which would be of value to practicing American physicians”
- Classifies spread from primary site to distant sites
  - T -- extent of primary tumor
  - N -- degree of involvement of regional nodes
  - M --existence of distant metastasis

The Clinical Biology of Cancer

- Manifested by both structural form of the tumor and physiological function in the patients
- Functional effects -- type, duration, and severity of cancer symptoms (e.g., weight loss, fatigue)
- Comorbidity -- Although unrelated to the cancer itself, the patient's coexistent disease can affect the choice of treatment and prognosis

- In many cancers, comorbidity prognostically more important than tumor size or TNM stage
- Particularly important for slow growing cancers and cancers which affect older people
  - For example: breast; prostate; oral cavity, pharynx and larynx; bladder; ovary; uterus; and non-Hodgkin's lymphoma

- Based on recent cancer incidence rates, these cancers represent approximately two-thirds of all adult cancers
- While the importance of comorbidity is obvious, the American Joint Committee Tumor, Node, Metastasis (TNM) staging system, NCI/SEER Program, and cancer registries do not include this information

Comorbidity Instruments

- Several instruments have been developed to classify different comorbid diseases and to quantify the severity of the overall comorbid condition
- None of the instruments were specifically designed to study comorbidity in cancer patients
- Nevertheless, these instruments have been used to classify comorbidity in several types of cancers and have performed well

Kaplan-Feinstein Index

- Developed from the study of comorbidity in patients with diabetes mellitus
- The KFI has been used to study the impact of comorbidity in several cancers
- Specific diseases and conditions are classified into four groups-- none, mild, moderate, or severe according to severity of organ decompensation and prognostic impact

Kaplan, Feinstein. *J Chron Dis.* 1974;27:387-404

Example

Congestive Heart Failure

- Mild – Exertional or paroxysmal dyspnea which has responded to treatment
- Moderate – Hospitalized more than six months ago
- Severe – Hospitalized within last 6 months or ejection fraction < 20%

Overall Comorbidity Score

- Highest ranked single ailment
- In cases where two or more Moderate ailments occur in different organ systems, the Overall Comorbidity Score should be designated as Severe

Example

CONDITION	DECOMPENSATION
Myocardial Infarct more than 6 months ago	Moderate
DBP 90-114 mm Hg	Mild
History of alcohol abuse, but not presently drinking	Mild
Overall Comorbidity Score	Moderate

Example

CONDITION	DECOMPENSATION
Chronic exertional angina	Moderate
Major depression controlled with medication	Mild
Diabetes requiring insulin	Moderate
Overall Comorbidity Score	Severe

Modified Kaplan-Feinstein Index

- KFI modified for two important reasons:
  1. Did not include diabetes since this was index disease
  2. Did not include several other important conditions. For example, AIDS and dementia

- The investigators sought advice from clinical experts and the published literature to assign levels of comorbidity to the ailments not included in KFI

Comorbidity and Head and Neck Cancer

- Prognosis
- Treatment Selection

- Data presented here derive from research conducted in the Clinical Outcomes Research Office at Washington University and funded through NCI/ACS
- To develop improved prognostic staging systems for evaluation of treatment effectiveness
- Retrospective review of the records of patients with newly diagnosed squamous cell carcinomas of the oral cavity, oropharynx, and larynx

- Patients first treated at Washington University Medical Center between 1980 and 1990
- *Prognostic* comorbidity is Severe Kaplan-Feinstein comorbidity
- Main outcome measure is five-year survival; secondary outcome measure is overall survival

Comorbidity and Prognosis

- Prognostic estimates for patients with head and neck cancer are often based solely on the TNM stage of the tumor
- However, five-year survival rates are also associated with the severity of comorbidity
- Survival rates are lower for patients with prognostic comorbidity than for patients without prognostic comorbidity
- This relationship is independent of TNM stage

FIVE-YEAR SURVIVAL RATES AS A FUNCTION OF COMORBIDITY SEVERITY AND SITE

Prognostic Comorbidity	Oral Cavity***	Oropharynx**	Larynx***	Total***
Absent	136/277 (49%)	111/290 (38%)	233/382 (61%)	480/949 (50%)
Present	2/21 (10%)	7/41 (17%)	17/48 (35%)	26/110 (24%)
Total	138/298 (46%)	118/331 (36%)	250/430 (58%)	506/1059 (48%)

Numerator = number of five-year survivors
Denominator = total number of patients in each cell
Survival between two comorbidity groups statistically different at:
* $p < 0.05$ **$p < 0.01$ ***$p<0.001$

Comorbidity and Treatment Selection

- For many advanced head and neck cancer patients, initial treatment involves combined surgery and radiation therapy
- Patients with severe comorbidities often deemed "too sick" to tolerate surgery, recommended to receive radiation therapy only
- Impact of comorbidity on initial treatment selection is demonstrated by comparing the rate of utilization of radiation therapy alone versus the rate of combined radiation therapy and surgery for patients with Stage III and IV carcinomas

THE IMPACT OF COMORBIDITY ON THE USE OF RADIATION THERAPY ONLY AS INITIAL TREATMENT FOR 356 PATIENTS WITH STAGE III/IV DISEASE OF LARYNX, ORAL CAVITY AND OROPHARYNX

Prognostic Comorbidity	Initial Treatment Radiation Therapy Only	Odds Ratio (95% CI)
Absent	84/311 (27%)	1.0
Present	23/45 (51%)	3.02 (1.61-5.69)
Total	107/356 (30%)	

107 patients received radiation only
Numerator = number of patients who received radiotherapy only
Denominator = total number of patients with Stage III/IV disease in each cell

Interaction Between Comorbidity, Treatment, and Survival

- Is the observed decrease in survival for patients with prognostic comorbidity actually due to less aggressive treatment?
- Cox Proportional Hazards analysis performed to examine independent impact of comorbidity on survival
- Null hypothesis: After controlling for tumor site, size, and initial treatment, comorbidity has no impact on survival

Cox Proportional Hazards Model

Variable	Category	Risk Ratio	95% CI	p Value
Site	Larynx	1	--	--
	Oral Cavity	1.230	1.022-1.479	0.0283
	Orophrynx	1.127	0.947-1.340	0.1776
TNM	Stage I	1	--	--
	Stage II	1.267	1.003-1.600	0.0472
	Stage III	1.787	1.421-2.248	0.0001
	Stage IV	2.758	2.177-3.492	0.0001
Prognostic Comorbidity	Absent	1	--	--
	Present	1.462	1.176-1.818	0.0006

Incorporation of Additional Variables To Cancer Staging System

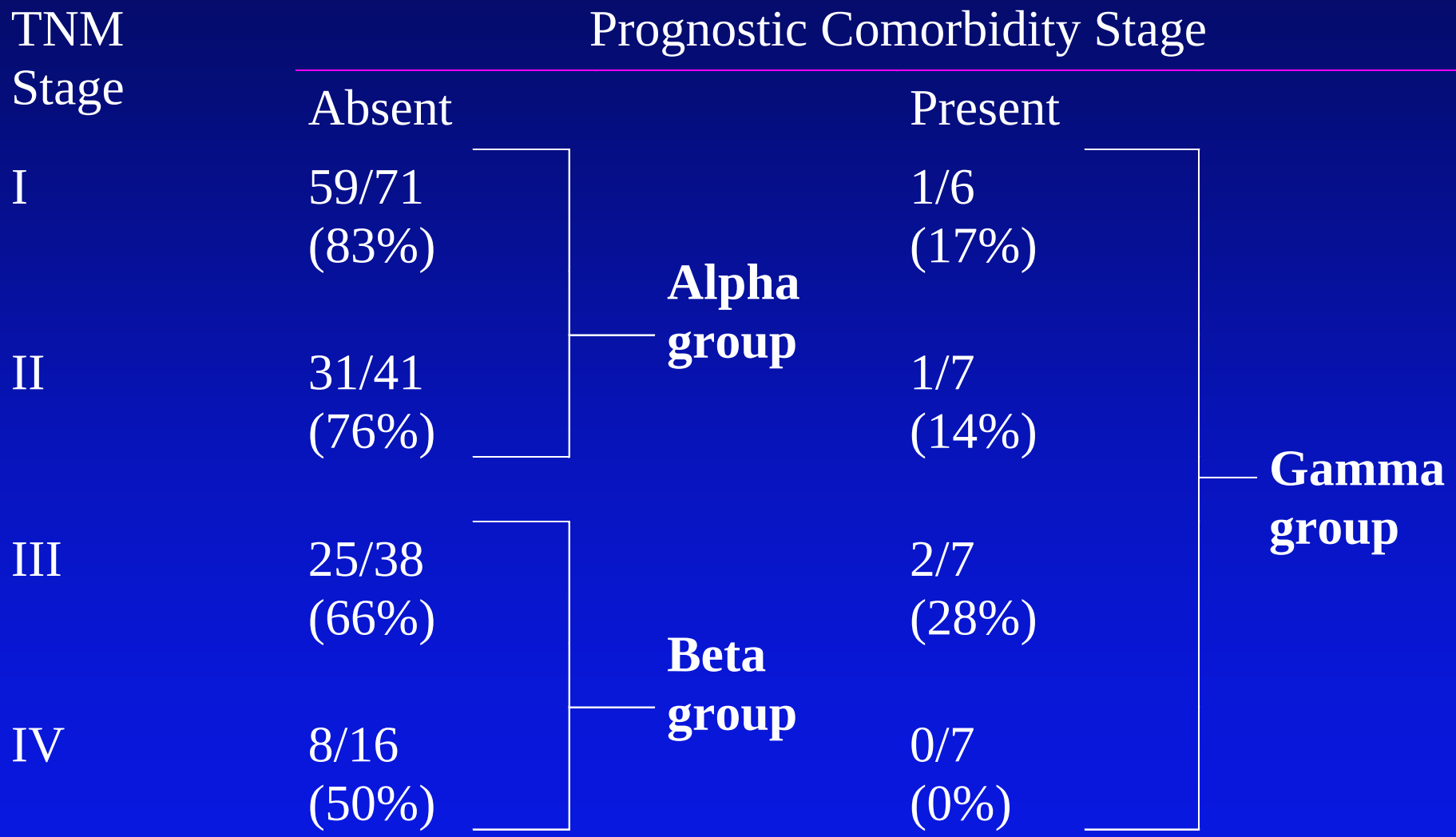
- Because TNM system is based on a bin model, the number of bins increases as additional prognostic variables are added
- Inclusion of new factors deemed impractical
- Conjunctive consolidation, a different form of multivariable analysis, can be used to incorporate additional prognostic variables without relying on cryptic mathematical equations or additional bins.

5-Yr. Survival Rates in Patients with Laryngeal Cancer: Conjunction of TNM and Prognostic Comorbidity

TNM* Stage	Prognostic Comorbidity Stage		
	Absent	Present	Total
I	59/71 (83%)	1/6 (17%)	60/77 (78%)
II	31/41 (76%)	1/7 (14%)	32/48 (67%)
III	25/38 (66%)	2/7 (28%)	27/45 (60%)
IV	8/16 (50%)	0/7 (0%)	8/23 (35%)
Total	123/166 (74%)	4/27 (15%)	127/193 (66%)

* X^2 for linear trend = 15.6; $p < .01$
Denominators: number of patients in each category
Numerators: corresponding number of 5-year survivors

5-Yr. Survival Rates in Patients With Laryngeal Cancer: Consolidation of TNM and Prognostic Comorbidity



Denominators: number of patients in each category.
Numerators: corresponding number of 5-year survivors

5-Yr. Survival Rates in Patients With Laryngeal Cancer, According to Composite Staging System

Stage*	5-Year Survival
Alpha	90/112 (80%)
Beta	33/54 (61%)
Gamma	4/27 (15%)
Total	127/193 (66%)

* X^2 for linear trend = 42.2; $p < .001$
Denominators: number of patients in each category
Numerators: corresponding number of 5-year survivors

The Head and Neck Cancer Patient Education and Decision-Making Program

- Interactive Teaching Segment
- Prognostic Component

Prognostic Component

- Individualized survival rates based on comparison of demographic information
- Survival estimates for age, gender, race-matched peers derived from the Office of Vital Statistics
- Capable of over 4500 unique prognostigrams

Prognostic Component

- Retrospective medical record review of 1151 patients
- Patients treated for initial squamous cell carcinoma of oral cavity, oropharynx or larynx
- Full five year follow-up obtained on 98% of the cohort
- Data analyzed with respect to the prognostic impact of age, race, gender, comorbidity, cancer-related symptom severity, tumor site and TNM stage

Unique Program Features

- Prognostic estimates based on more than just morphology
- Survival data compared to age, gender, race-matched peers
- Data available for three different types of patients
- Data for new patients can be displayed in three different ways

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http://oto.wustl.edu/clinepi/education/

Demonstration

Summary

- TNM divides patients into stages based on the morphologic extent of tumor
- Despite a distinctive prognostic gradient, each stage contains a prognostically heterogeneous group of patients
- Survival rates within each stage can vary dramatically according to clinical features

- New taxonomies can facilitate a scientific classification for pertinent clinical variables
- Conjunctive consolidation can enable clinical variables to be incorporated without expanding the total number of stages
- Anatomic extent of cancer is only one factor in the medical decision-making process for patients

- The scientific evaluation of prognosis and treatment is impeded by rigid adherence to a system based solely on anatomic descriptions of the cancer, while excluding suitable descriptions of the patient

- A prime scientific challenge in current cancer staging is to incorporate the omitted patient-based variables to produce a useable, improved clinical system cancer