Epidemiology of Cancer-Related Symptoms

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Definition of Symptoms

- Greek word--"symptoma--anything that has befallen one"
- Webster-- "the subjective evidence of disease or physical disturbance observed by a patient"
- Implicit--subjective and negative nature of symptoms

Cleeland and Reyes-Gibby, 2002

Why Study Symptoms?

- **Moral imperative—prevent suffering, adverse impact on function and quality of life.** Compared to patients without persistent pain, pain sufferers were more likely to experience severe activity limitations (OR= 1.63; CI=1.41-1.89) (Gureje, et al., 1998)

- **Impact on health--Significant cause of morbidity in the United States.** 2.9 million Americans (1.1% of the population) are treated annually by chronic pain specialists (Marketdata, 1995) Pain was predictive for the development of depression (Magni, et al., 1994)

- **Health care cost-- in billions, health care utilization**

  Pain-relieving drugs was the second leading therapeutic class for drugs mentioned at office visits (2001 National Ambulatory Medical Care Survey) (Cherry, et al., 2003). Lost productive time from common pain conditions among active workers costs an estimated 61.2 billion dollars per year. (Stewart, et al, 2003)

How are symptoms measured?

- Psychometrics– science of measurement of psychological attributes (attitudes, beliefs, experience, etc.) rather than physical attributes (height, weight, etc.)

- Questionnaires/ instruments / tests / scales/ tools

How are symptoms measured?

- Reliability– measures consistently (internal consistency reliability; test-retest reliability; inter-rater reliability)

- Validity- measures what it is supposed to measure (content validity; construct validity; criterion validity)

How are symptoms measured?

- Select items from an item pool
  - based on clinical practice
  - based on literature review
- Select the type of response scale
- Establish the tool's reliability and validity

Response scales

Patient's Name _____ Date ___/___/___ ID # ____

MEMORIAL SYMPTOM ASSESSMENT SCALE – Short Form [MSAS-SF]

I. INSTRUCTIONS: Below is a list of symptoms. If you had the symptom DURING THE PAST WEEK, please check Yes. If you did have the symptom, please check the box that tells us how much the symptom DISTRESSED or BOTHERED you.

Check *all* the symptoms you have had during the PAST WEEK.	Yes [✓]	➔➔ IF YES: How much did it DISTRESS or BOTHER you? Not at All [0]	A little Bit [1]	Some-what [2]	Quite a Bit [3]	Very Much [4]
Difficulty concentrating						
Pain						
Lack of energy						
Cough						
Changes in skin						
Dry mouth						
Nausea						
Feeling drowsy						
Numbness/tingling in hands and feet						
Difficulty sleeping						
Feeling bloated						
Problems with urination						
Vomiting						
Shortness of breath						
Diarrhea						
Sweats						
Mouth sores						
Problems with sexual interest or activity						
Itching						
Lack of appetite						
Dizziness						
Difficulty swallowing						
Change in the way food tastes						
Weight loss						

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Portenoy, et al, 1994

Anderson Symptom Assessment System

Please circle the number that best describes:

No Pain	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Pain
Not Tired	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Tiredness
Not Nauseated	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Nausea
Not Depressed	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Depression
Not Anxious	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Anxiety
Not Drowsy	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Drowsiness
Best Appetite	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Appetite
Best Feeling of Wellbeing	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Feeling of Wellbeing
No Shortness of Breath	0 1 2 3 4 5 6 7 8 9 10	Worst Possible Shortness of Breath
Other Problem	0 1 2 3 4 5 6 7 8 9 10	

Bruera, et al, 1994

Examples of Symptom Scales

	Number of Items	Dimensions	Rating
Multisymptom assessment			
Symptom distress scale (SDS)[6]	13	Severity	1–5 Likert-type scale, with 5 indicating the most distress
Memorial symptom assessment scale (MSAS)[4]	32	Frequency, severity, distress	1–4 Likert-type scale, with 4 indicating the highest rating
Rotterdam symptom checklist (RSC)[5]	38	Severity and impairment	4-point Likert-type scale (not at all, a little, quite a bit, very much)
Edmonton symptom assessment system (ESAS)[2]	10	Severity	Visual analogue scale 0–100 or numeric rating scale 0–10
M D Anderson symptom inventory (MDASI)[3]	19	Severity and interference	Numeric rating scale 0–10
Quality of life			
Quality-of-life questionnaire (EORTC-QLQ-C30)[7]	30	Severity, functional effect, global-health status	4-point Likert-type scale (not at all, a little, quite a bit, very much)
Short form 36 (SF-36)[8]	36	Eight domains, including pain, fatigue or energy, and psychological distress	5-point Likert (all of the time to none of the time)
Functional assessment of cancer therapy (FACT)[9]	Module-specific	Several domains including symptoms	5-point scale from 0 (not at all) to 4 (very much)

Table 1: Multisymptom assessment and quality of life scales

Cancer-related Symptoms

- May occur in relation to disease progression or a complication of the illness or its treatment. For example, most chronic pain in cancer patients is a consequence of cancer treatment.

- Chemotherapy--painful peripheral neuropathy from chemotherapeutic agents such as vincristine, platinum, taxanes, thalidomides, bortezimib and other agents; cognitive impairment, etc.

- Radiation--Radiation-induced neural damage including radiation-induced brachial plexopathy and post-radiation pelvic pain syndrome

- Post-surgical pain syndromes from post-mastectomy, post-amputation, and post-thoracotomy.

Nationally-representative Sample Pain, Depression, Fatigue

Table 2

Prevalence of Pain, Depression, and Fatigue ($n = 17,210$)[a]

Symptoms	With a History of Cancer, % ($n = 2,161$)	Without a History of Cancer, % ($n = 15,049$)	*P* Value
Pain[b]	33 (712)	29 (4323)	0.0001
Depression[b]	21 (409)	18 (2374)	0.0001
Fatigue[b]	25 (545)	18 (2685)	0.0001

[a]HRS, Data 2000.
[b]Not mutually exclusive categories.

Table 4

Odds Ratios for Pain, Depression, and Fatigue in Community-Dwelling Adults With a History of Cancer Relative to Those Without a History of Cancer

			95% C.I.	
Symptoms	*P* Value	Odds Ratio	Upper C.I.	Lower C.I.
Pain	0.01	1.15	1.03	1.28
Depression	0.005	1.21	1.06	1.37
Fatigue	0.0001	1.45	1.29	1.63

HRS, Data 2000.
Note: All analyses were adjusted for age, gender, race, educational level, insurance status and coexisting medical conditions.
Separate analyses for each symptom.

* Reyes-Gibby et al, 2006;

Co-occurrence of Cancer-Related Symptoms

Table 2

Prevalence of Moderate to Severe Symptoms Before, During, and After Chemoradiation[a]

	Before Chemoradiation		During Chemoradiation[b]		After Chemoradiaton	
Number of Moderate to Severe Symptoms	*n*	%	*n*	%	*n*	%
0	21	58	14	34	20	66.7
1	6	16.8	5	12	4	13.3
2	1	2.8	1	2.4	3	10
3	2	5.6	6	14.6	0	0
4	2	5.6	0	0	2	6.6
5	1	2.8	2	5	0	0
6	1	2.8	4	10	1	3.3
7 or greater	2	5.6	9	22	0	0
Total	37	100	41	100	30	100

[a]Significant McNemar test ($P < 0.05$) for difference between proportion reporting two or more symptoms before and after chemoradiation.
[b]Prevalence during treatment was computed as number of patients reporting symptoms of >5 symptom severity during the chemoradiation period.

Reyes-Gibby, et al, 2007

Cancer-Related Symptoms

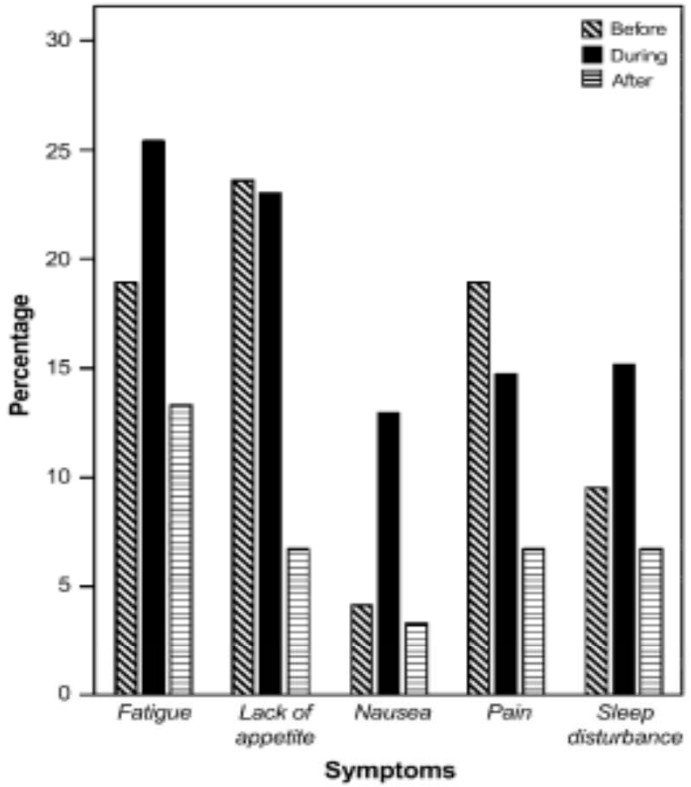

Fig. 2. Prevalence of moderate to severe symptoms (≥5, on a 0–10 scale) before, during, and after chemoradiotherapy ($n = 43$) (Note: all symptom items were statistically significant ($P < 0.001$) for McNemar test for paired binary response before and after chemoradiation ($n = 27$). No statistically significant ($P > 0.05$) differences for survival and disease progression for patients with complete data versus those with missing data Prevalence during treatment was computed as any report of >5 symptom severity during the chemoradiation period).

Reyes-Gibby, et al, 2007

Variations in Symptoms

- Disease-related (Stage of disease, Tumor location)
- Clinical health status (Co-morbid conditions)
- Socio-demographics (Age, Gender, Race/Ethnicity, Access to care)
- Treatment settings (Inpatient, Outpatient)
- Assessment of biological mechanisms

What Do Consensus Panels Say?

- Develop mechanism-based classifications to identify common biology
- Develop models to direct systematic research
- Explore qualitative and quantitative differences between cancer and non-cancer populations
- New treatments

NIH State of the Science Panel, 2003

Why look for genes associated with symptoms?

- Prediction/Risk Assessment
  - Prompt identification and treatment
- Understanding of Mechanisms
  - Direct New Therapeutic Approaches
- Targeted Therapy
  - Pharmacogenetics

Genetic variations in interleukin 8 and 10 are associated with pain, depressed mood, and fatigue in lung cancer patients

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Background

- Lung cancer is the most common fatal malignant neoplasm. Non Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer.
- Patients with NSCLC suffer from severe and debilitating symptoms associated with cancer and its treatment.
- Clinically symptoms are never expressed in isolation, but most studies examine symptoms as mutually exclusive entities.

World Health Organization, 2011

Immune Dysregulation and Cancer Symptoms

Symptoms	Associated Cytokines
Fatigue	IL-1, IL-6, IFN-α, TNF-α
Anorexia/cachexia	IL-1, IL-6, TNF-α
Fever	IL-1, IL-2, IL-6, IL-12, IFN-α, TNF-α
Depression	IL-1, IL-6, IFN-α, TNF-α
Sleep disorder	IL-6, TNF-α
Cognitive impairment	IL-1, IFN- α
Pain	IL-1, IL-6, IL-8, TNF-α, Nfkappa B, PTGS2

Kurzrock, 2001; Dantzer, 2004; Watkins, 2010; Reyes-Gibby, 2008, 2010

Purpose

We applied novel multivariate statistical methods to assess whether variants of 37 inflammation genes may serve as biologic markers of risk for severe pain, depressed mood, and fatigue in non-Hispanic white patients with non-small cell lung cancer.

Is there a common biological mechanisms for cancer-related symptoms?

Study Population

- Sample drawn from a large epidemiologic study of NSCLC
- Histologically-confirmed primary lung cancer
- Newly diagnosed; no prior chemoradiation or radiotherapy
- Caucasian

Symptom Assessment

- Upon presentation and prior to cancer treatment
- Pain was assessed using an 11-point numeric scale, (0= 'no pain' and 10= 'worst pain')
- "During the past 4 weeks, have you had a lot of energy? Have you been feeling downhearted and blue?"
- Response options were as follow: none of the time; little of the time; some of the time; good bit of time; most of the time; and all of the time.

Symptom Assessment

- Upon presentation and prior to cancer treatment
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Molecular Analysis

- SNPs in immune response pathways that met at least two of the following criteria:
- a) Minor allele frequency of at least 5%
- b) Location in the promoter, untranslated region, or coding region
- c) Reported association with symptoms

Inflammation Genes

- Pro-inflammatory cytokines and related molecules: IL1a, IL1b, IL2, IL6, IL8, IL12, IL16, TNF a, TNF b, GM-CSF, MCP, MIF, INFg
- Anti-inflammatory cytokines and related molecules: IL1ra, IL4, IL4R, IL-10, IL-10 RA, IL-10 RB, IL13
- Prostaglandin and Nitric Oxide: PTGS2, ENOS, INOS
- Intracellular signaling molecules: IKB, PPARA, PPARD, PPARG

Study Variables

Outcome: Severe Pain= a cut-off score of ≥ 7 (0 to 10 rating scale)
Severe Depressed mood and fatigue=combined the following response options "most of the time; all of the time"

Primary Independent: Assuming a dominant model for all SNPs

Covariates: Stage of disease, sex, comorbidities (no treatment data since all were collected prior to any therapy) were abstracted from patients' charts

Study Population

Variable	Pain (17%)		Fatigue (43%)		Depressed mood (7%)	
	Severe /non-severe	P-value	Severe/ Non-severe	P-value	Severe /non-severe	p-value
Age: >50	65/400		195/270		31/434	
<=50	32/102	0.007	65/69	0.18	13/121	0.24
Sex: Male	43/273		132/184		18/298	
Female	54/229	0.07	128/155	0.39	26/257	0.11
Stage of Disease: Early	32/253		109/176		23/262	
Late	62/225	0.001	140/147	0.01	19/268	0.51
Heart Disease: Yes	24/104		62/66		12/116	
No	59/321	0.39	165/215	0.32	26/354	0.35
Hypertension: Yes	29/159		78/110		13/175	
No	54/266	0.67	149/171	0.27	25/295	0.71
Stroke: Yes	4/19		12/11		4/19	
No	79/406	0.89	215/270	0.46	34/451	0.08

Correlation

	Pain	Depressed mood	Fatigue
Pain	1	0.294	0.385
Depressed mood	0.294	1	0.495
Fatigue	0.385	0.495	1

All significant at $p<0.001$

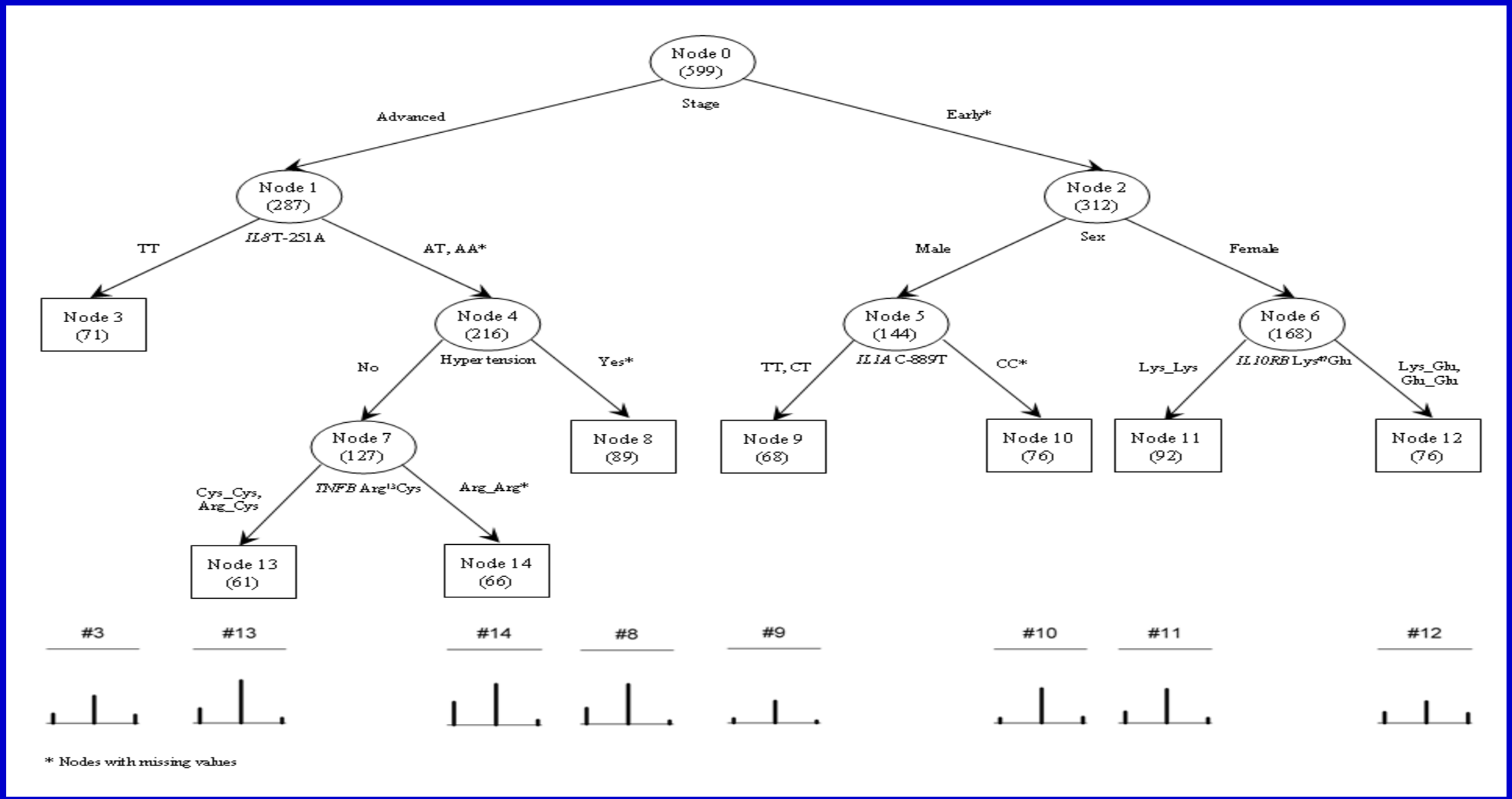
Classification and Regression Tree

- CRT is a stepwise, nonparametric procedure that uses exhaustive computerized searches and sorting techniques that classifies subjects into several homogenous subgroups and produces a tree structured output.

- A parent node always splits into two child nodes and the procedure is repeated for each child node. Each node splits only on one covariate and each splitting will produce mutually exclusive subgroups.

- Originally developed as classification/regression tree for a univariate discrete and continuous response, this method was later extended to handle multiple correlated binary outcomes.

Generalized Classification Tree



Advanced Stage of Disease

- Among patients with advanced-stage disease, IL-8, T251-A was the most relevant genetic factor for pain (OR=2.18, 95% confidence interval (CI)=1.34,3.55;p=0.001), depressed mood (OR=0.37; 95%CI=0.14,1.0), and fatigue (OR=2.07; 95%CI=1.16,3.70).

- This indicates that there is a joint effect between IL-8-T251A and advanced stage of lung cancer.

Early Stage of Disease

- Among those with early-stage NSCLC, variants in IL-10 receptor was relevant for fatigue among women. Specifically, women with genotype Lys_Glu or Glu_Glu in the IL-10 gene had a 0.49 times lower risk of severe fatigue compared to those with genotype Lys_Lys (OR=0.49, 95% CI=0.25,0.92; p=0.027).

- Among men with early-stage lung cancer, a marginal significance was observed for *IL1A* C-889T, CC or TT genotype had lower risk of severe fatigue compared with those with genotype CC (OR=0.38, 95% CI=0.13,1.06).

- This observation indicates that there is a joint effect of sex and genetic polymorphisms on symptoms in patients with early-stage disease

Conclusion

Variation in inflammatory response could partly explain variability in symptom burden among patients with lung cancer.

Symptoms are complex traits involving multiple genes. The interaction of genes with environmental factors (non-genetic variables) and with other genes influence symptom severity.

Genetic polymorphisms are stable markers and easily and reliably assayed, and therefore, could potentially help identify patients who might benefit most from symptom intervention.

Genotyping could become an integral component of an individualized treatment program for cancer patients.

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