

**Prognostic value of ER, PR, and HER2  
breast cancer biomarkers and AJCC's  
TNM staging system on overall  
survival of Caucasian females with  
breast cancer – an institution's 10 year  
experience**

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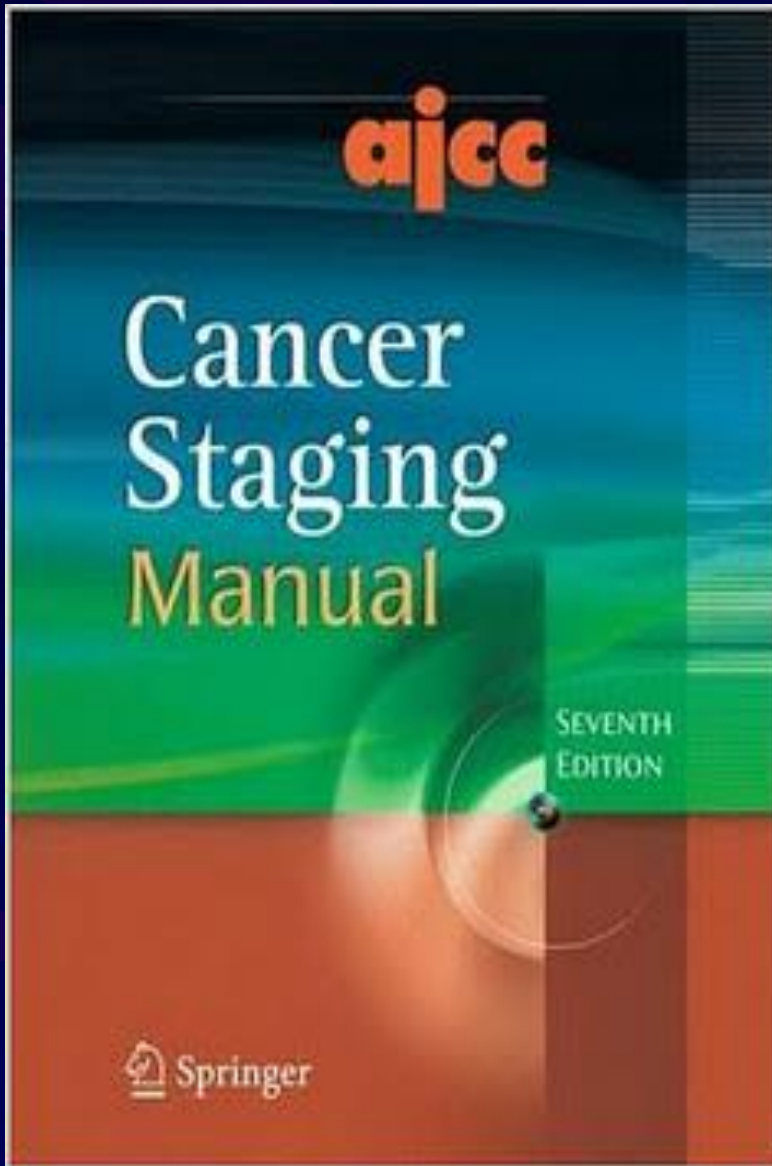
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# Introduction



## ANATOMIC STAGE • PROGNOSTIC GROUPS

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
<input type="checkbox"/> 0	Tis	N0	M0	<input type="checkbox"/> 0	Tis	N0	M0
<input type="checkbox"/> IA	T1*	N0	M0	<input type="checkbox"/> IA	T1*	N0	M0
<input type="checkbox"/> IB	T0	N1mi	M0	<input type="checkbox"/> IB	T0	N1mi	M0
	T1*	N1mi	M0		T1*	N1mi	M0
<input type="checkbox"/> IIA	T0	N1**	M0	<input type="checkbox"/> IIA	T0	N1**	M0
	T1*	N1**	M0		T1*	N1**	M0
	T2	N0	M0		T2	N0	M0
<input type="checkbox"/> IIB	T2	N1	M0	<input type="checkbox"/> IIB	T2	N1	M0
	T3	N0	M0		T3	N0	M0
<input type="checkbox"/> IIIA	T0	N2	M0	<input type="checkbox"/> IIIA	T0	N2	M0
	T1*	N2	M0		T1*	N2	M0
	T2	N2	M0		T2	N2	M0
	T3	N1	M0		T3	N1	M0
	T3	N2	M0		T3	N2	M0
<input type="checkbox"/> IIIB	T4	N0	M0	<input type="checkbox"/> IIIB	T4	N0	M0
	T4	N1	M0		T4	N1	M0
	T4	N2	M0		T4	N2	M0
<input type="checkbox"/> Stage IIIC	Any T	N3	M0	<input type="checkbox"/> Stage IIIC	Any T	N3	M0
<input type="checkbox"/> Stage IV	Any T	Any N	M1	<input type="checkbox"/> Stage IV	Any T	Any N	M1

\* T1 includes T1mi

\*\* T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

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# Introduction

- Measuring the Estrogen Receptor (ER), Progesterone Receptor (PR) and Epidermal Growth Factor Receptor 2 (HER2) is standard of care for breast cancer management<sup>1</sup>
- **Recent Proposals:** Inclusion of biomarkers into the TNM system (bTNM) improves the TNM accuracy for staging, prognosis, and treatment<sup>2-4</sup>

1. Edge SB, et al. *AJCC Cancer Staging Manual*. 7th ed. New York: Springer; 2010.
2. Bagaria, S et al. *JAMA Surg*. doi:10.1001/jamasurg. 2013. 3181.
3. Veronesi, U et al. *The Breast Journal* 2009;15:291-5
4. Jeruss, J et al. *J Clin Oncol*. 2011;29:4654-61



# Introduction

- Our initial study<sup>5</sup> on 595 Caucasian patients with invasive breast carcinoma (2000-2004):
  - TNM status and age were significant predictors of overall survival
  - ER/PR/HER2 expressions were not predictive when using the St. Gallen five-group ER/PR/HER2 subtype classification<sup>6</sup>.

5. Ferguson, NL et al. *The Breast Journal*. 2013;19:22-30



# Introduction

- Our recent study<sup>7</sup>: What is the relevance of the tumor biomarkers in the recently proposed bTNM classification system<sup>2</sup> in which the inclusion of triple negative ER/PR/HER2 phenotype (**TNP**) could improve the prognostic accuracy of TNM?
- One of our ongoing studies: Can classification system that uses only ER biomarker status, but also incorporates grade into the TNM stage improve prognostic accuracy of TNM?

2 Bagaria, S et al. *JAMA Surg.* *JAMA Surg.* 2014; 149(2):125-9

7. Orucevic, A et al. *The Breast Journal.* 2015; 21(2):147-154.

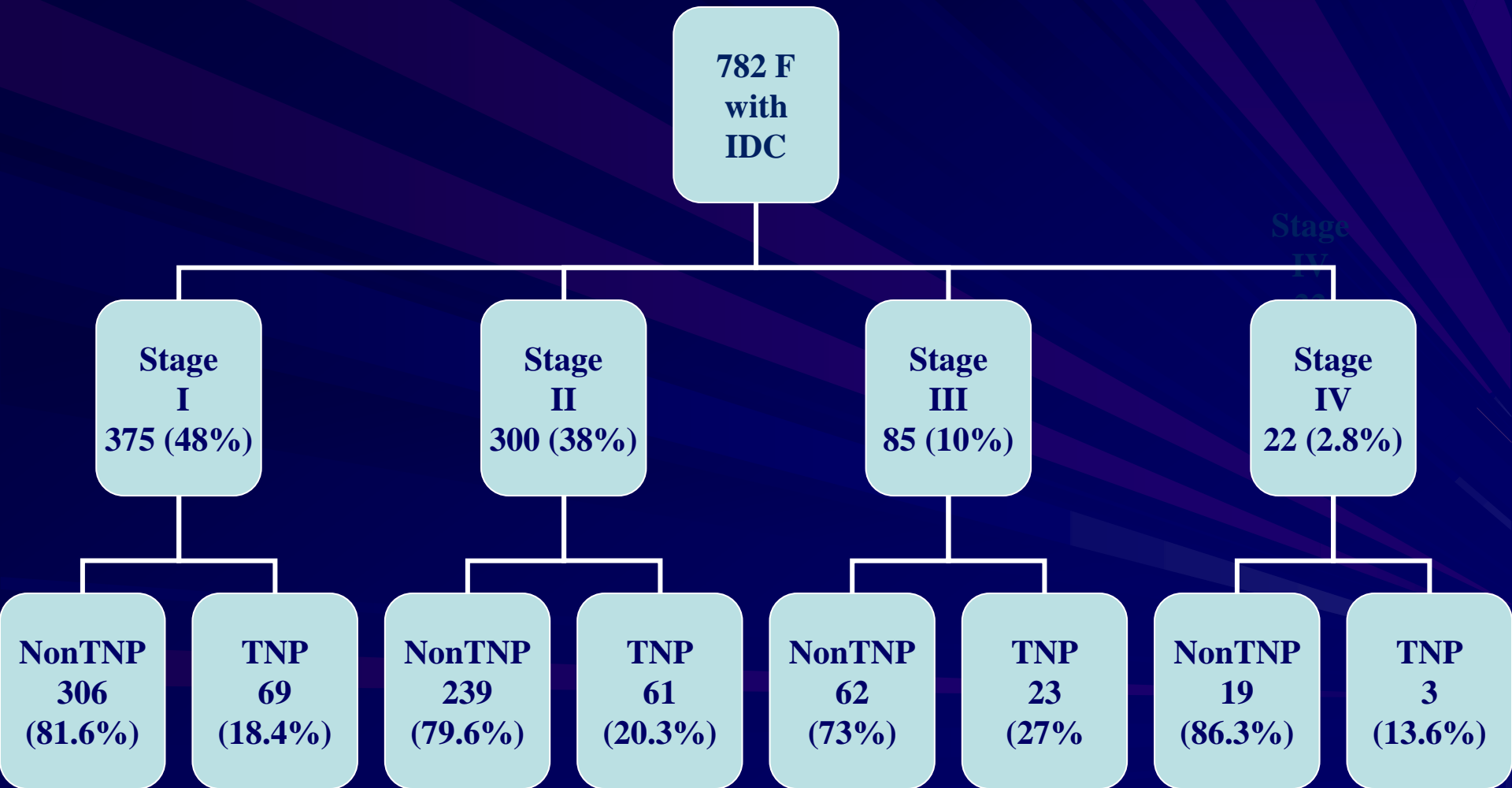
8. Yi, M et al. *J Clin Oncol.* 2011

# Methods (TNP vs nonTNP)

- From 791 Caucasian women diagnosed with primary invasive ductal carcinoma from 1/1998-7/2008 (10 year period) 782 patients had complete data on TNM stage
- Patients were categorized according to their TNM stage and TNP vs. non-TNP phenotype
- The Overall Survival (OS) was measured comparing these categories using Kaplan Meier curves and Cox regression analysis



# Biomarkers and TNM Stage



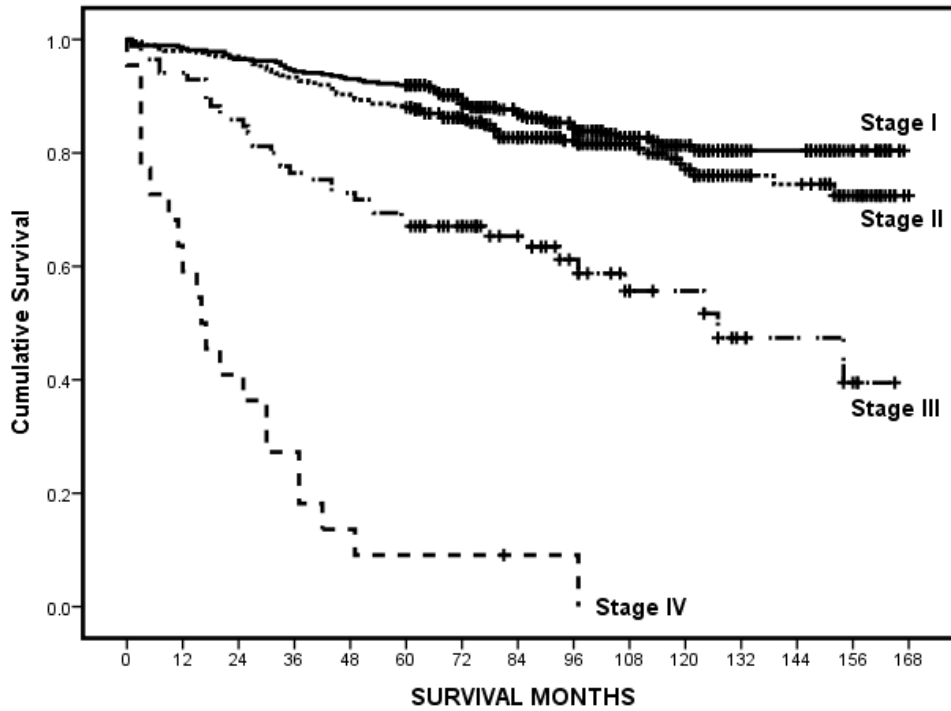
# Clinico-pathologic characteristics of patients with IDC when divided by the TNM stage and TNP and Non-TNP ER/PR/HER2 phenotype

	Age*	Grade**	Nottingham Score**	Size (mm)*	Survival months*
Stage I Non-TNP	60.8	1	6	11.9	96.4
Stage I TNP	56.4	3	8	12.1	98.4
Stage II Non-TNP	57.8	2	7	26.1	96.0
Stage II TNP	52.5	3	8	28.7	93.3
Stage III Non-TNP	56.7	3	8	36.9	78.9
Stage III TNP	54.8	3	8	39.6	64.1
Stage IV Non-TNP	61.4	2	7	28.3	27.7
Stage IV TNP	47.6	3	8	16.0	5.6

**Table legend:** \* = mean value; \*\* = most frequent



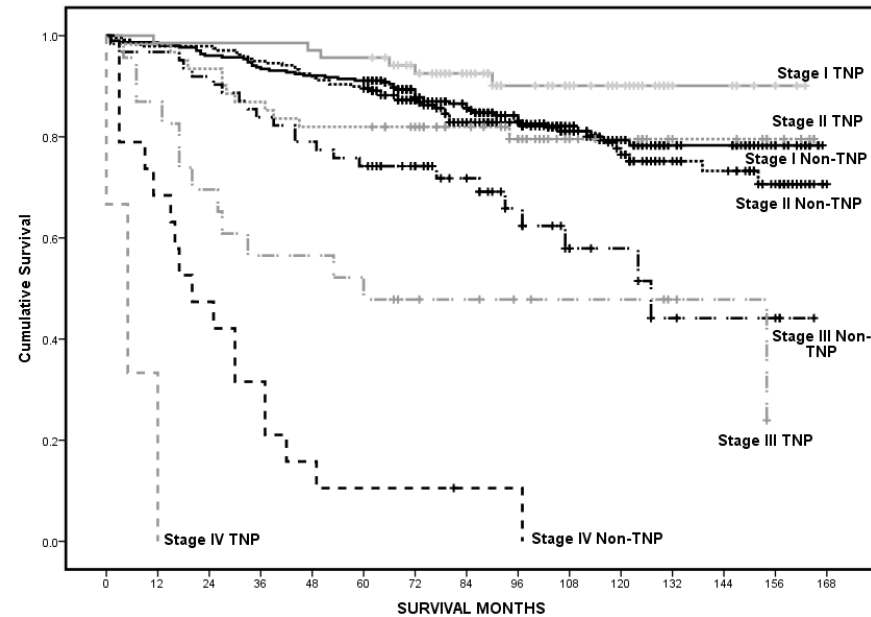
# Kaplan Meier Survival Curves



Note: + = Censored

**bTNM**

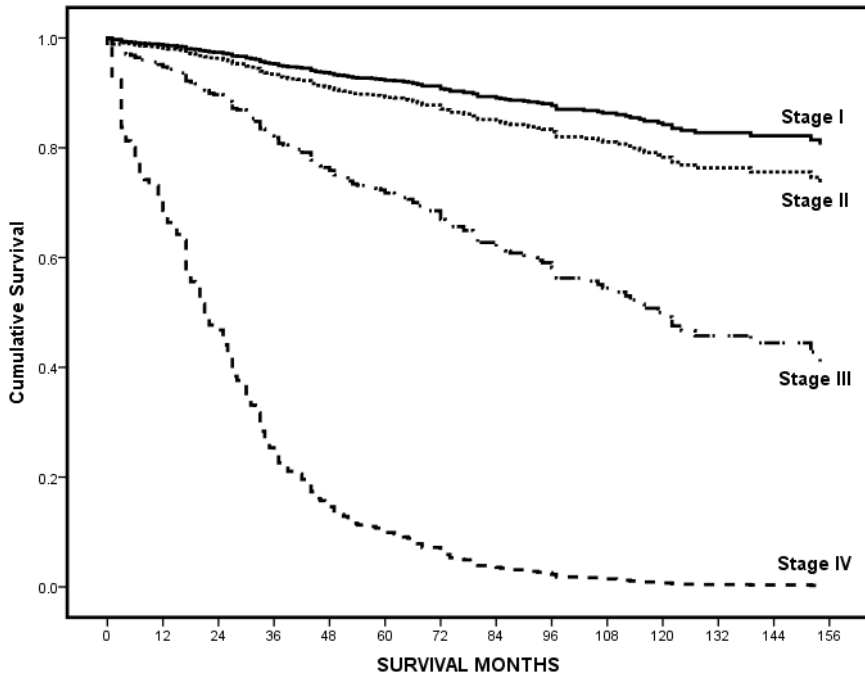
**TNM**



Note: + = Censored

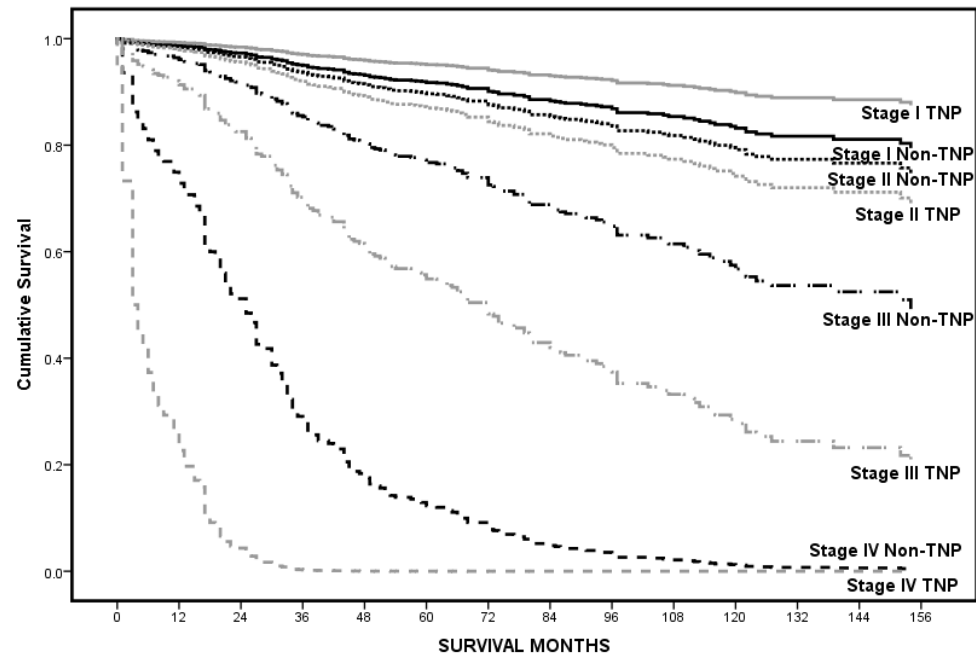


# Cox Regression Analyses



**bTNM**

**TNM**



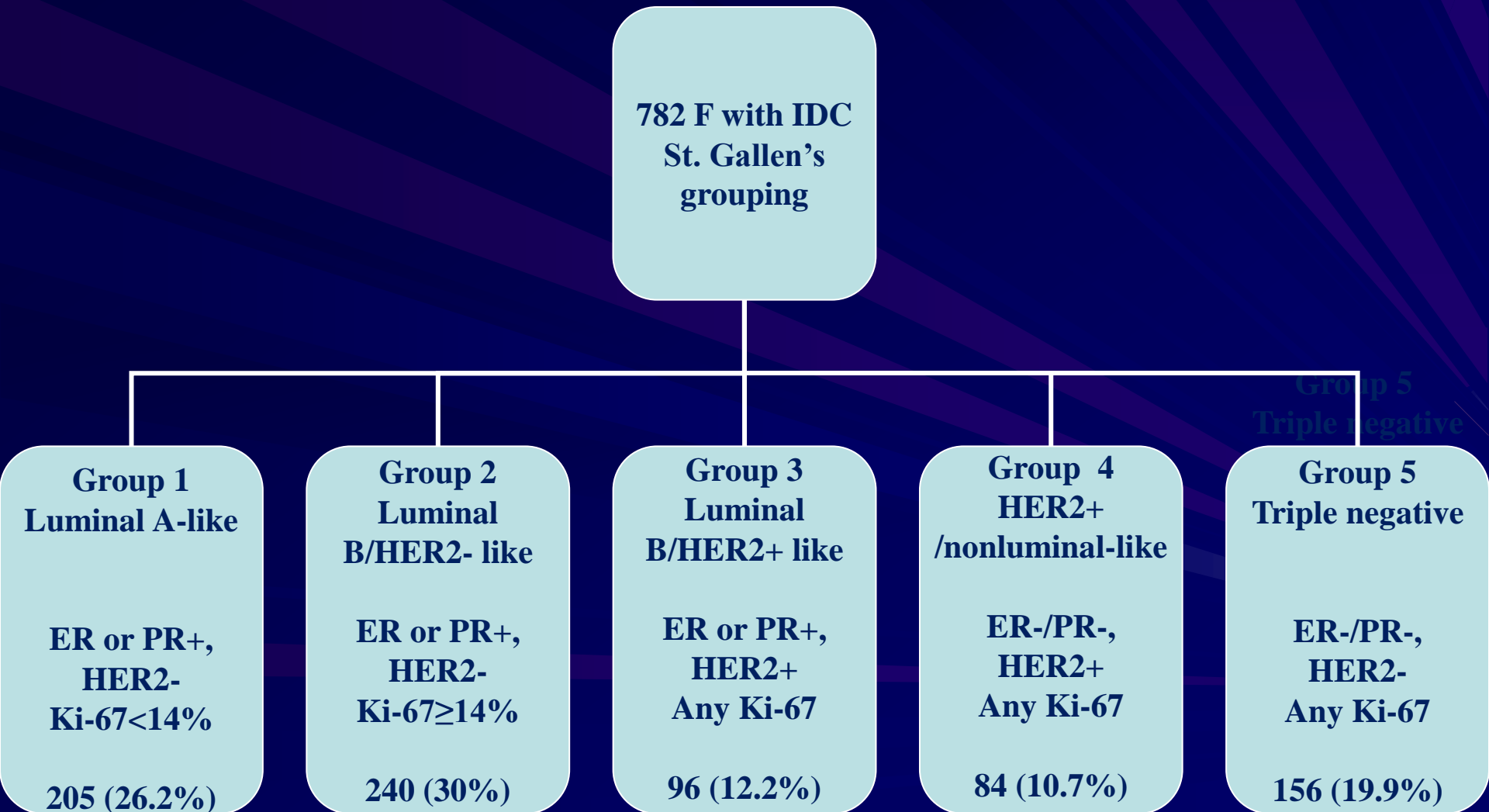
# Summary of Results

- **TNM stage and age are predictive of OS**
  - Stage II = HR 1.41, 95%CI 1.01-1.97
  - Stage III = HR 3.96, 95%CI 2.68-5.88
  - Stage IV = HR 27.25, 95%CI 16.84-44.08

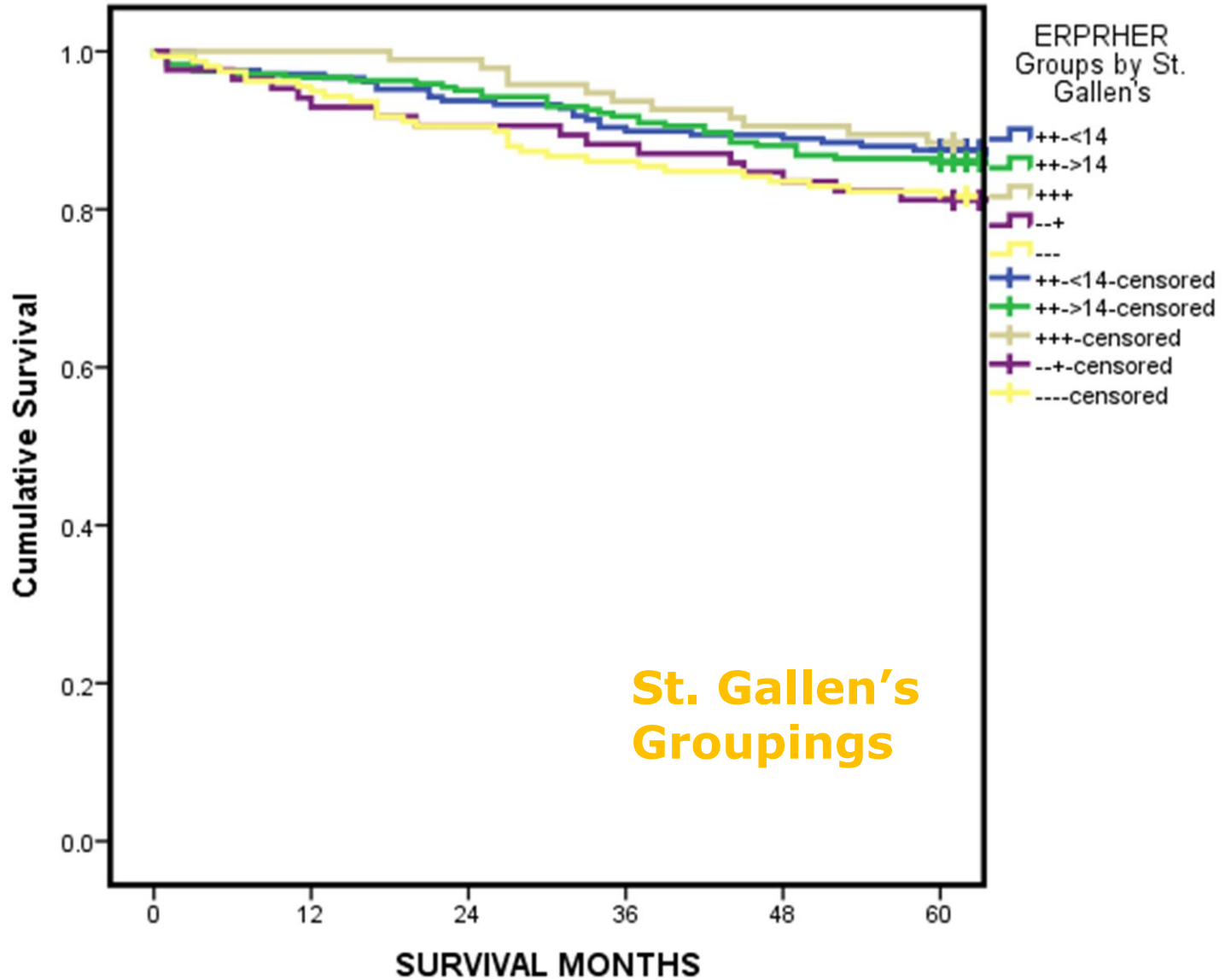
Age = HR 1.05, 95%CI 1.04-1.06
- **Adding TNP to TNM staging is predictive of OS only for higher TNM stages**
  - Stage III=HR 3.08, 95%CI 1.88-5.04
  - Stage IV=HR 24.36, 95%CI 13.81-42.99
- **No significant effect on TNM Stages I and II**



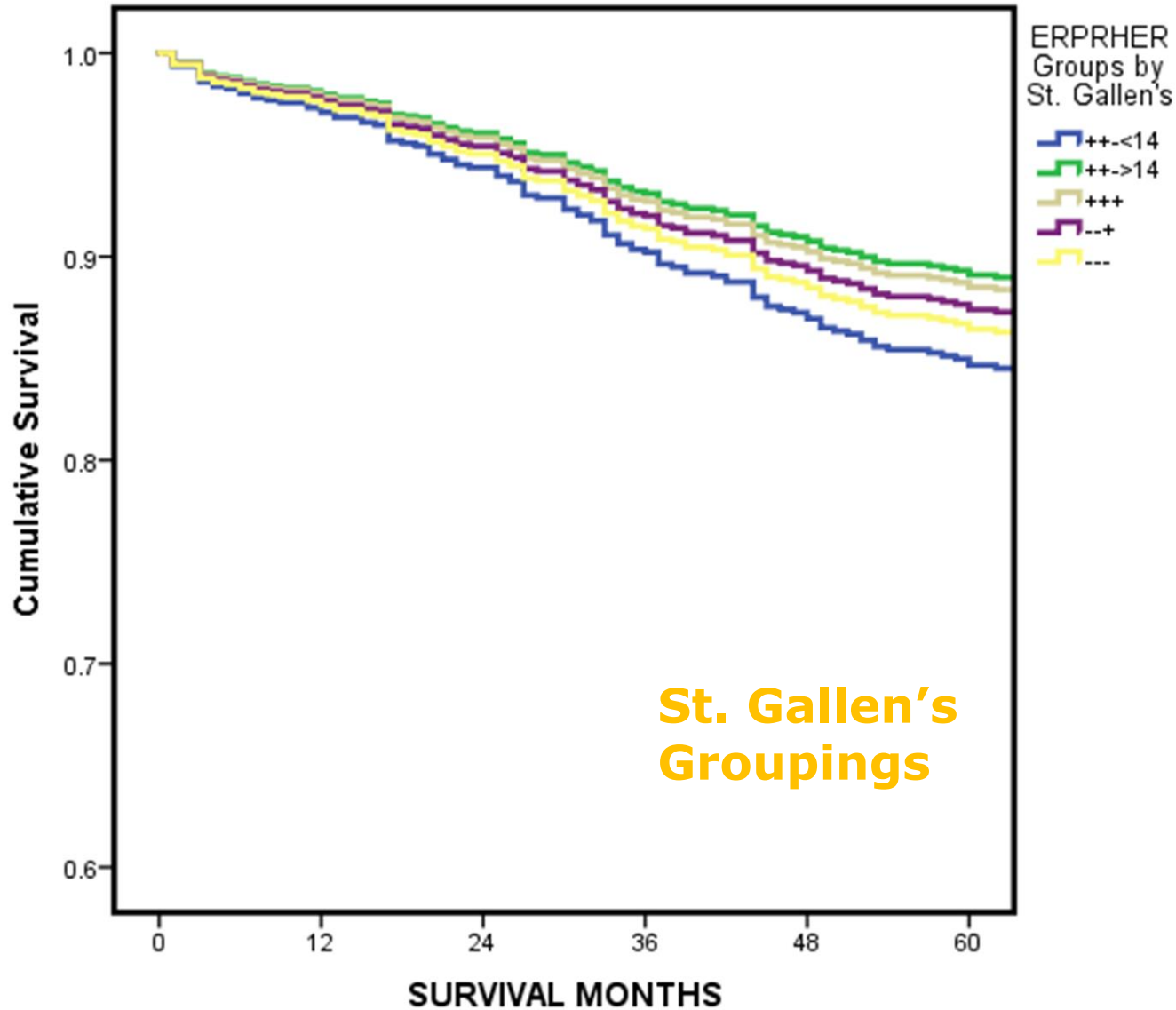
# Biomarkers with St. Gallen's Groups



# Kaplan-Meier curve



# Cox Regression Analysis



# Summary of Results

## St. Gallen ER/PR/HER2 grouping

- **The St. Gallen ER/PR/HER2 grouping had no significant impact on survival regardless of TNM stage or age**



# ER, Grade and TNM stage

- Incorporation of grade and ER status to pathologic TNM stage<sup>8</sup>

8. Yi, M et al. *J Clin Oncol*. 2011; 29:4654-4661



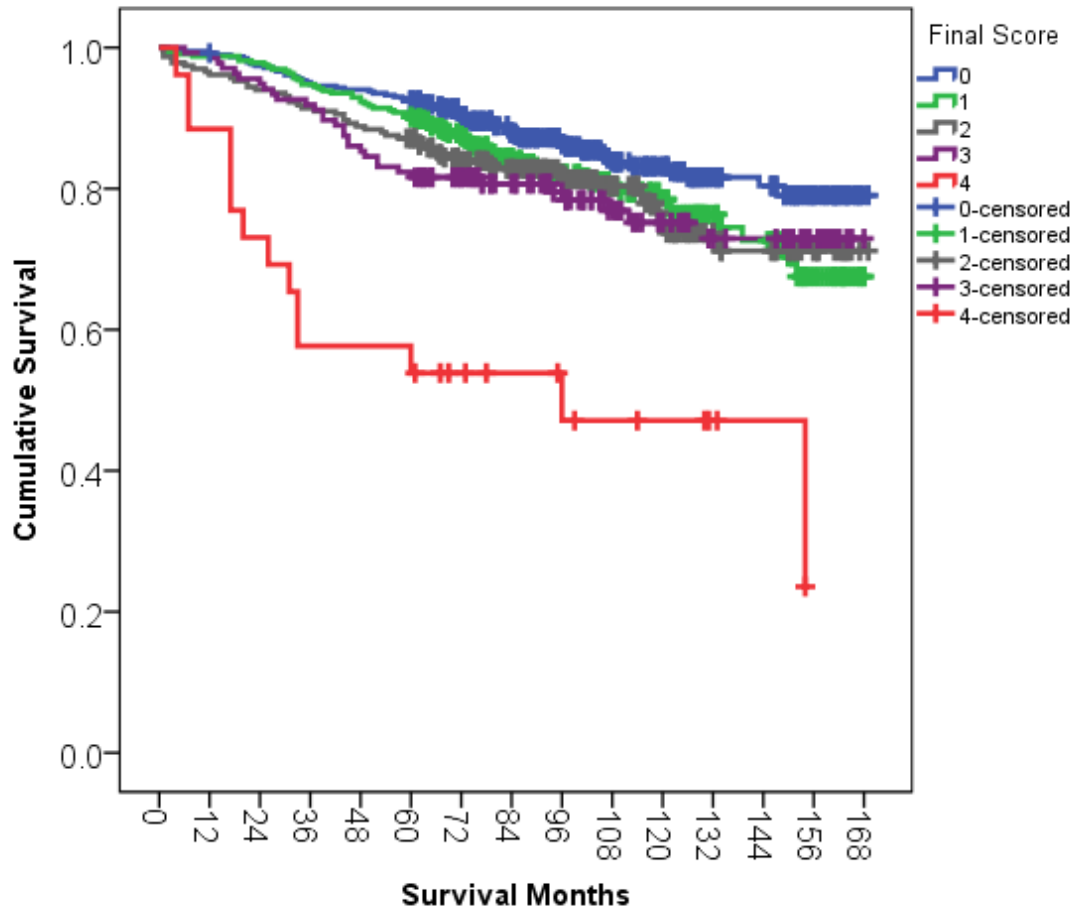
# ER, Grade and TNM stage

- Incorporation of grade and ER status to pathologic TNM stage<sup>8</sup>
- Final score = ER + Grade + Stage -> 0-4
  - ER
    - ER+ = 0
    - ER- = 1
  - Grade
    - Grade 1 & 2 = 0
    - Grade 3 = 1
  - Stage
    - Stage I = 0
    - Stage IIA & IIB = 1
    - Stage IIIA = 2

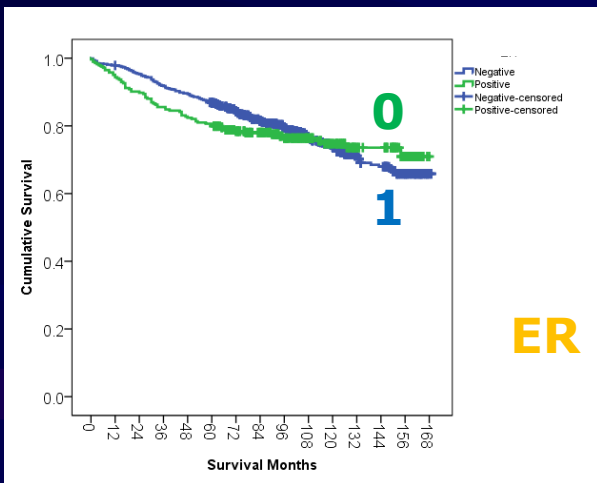
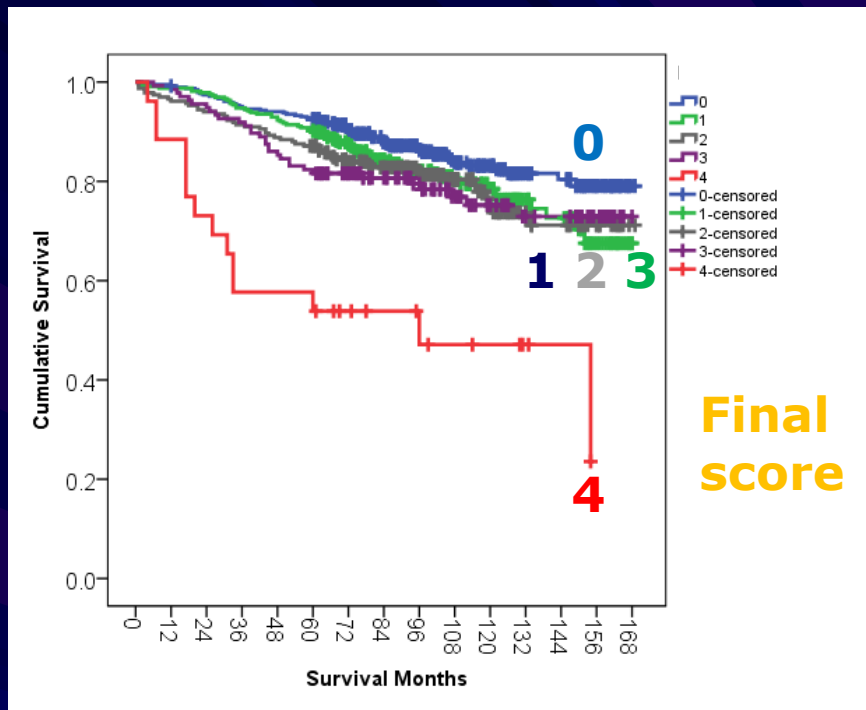
# Patients characteristics for Final Score ER + Grade + Stage

Final score	Total (N)	Dead (N)	Alive (N)	% Survival
0	387	58	329	85%
1	326	64	262	80.4%
2	233	48	185	79.4%
3	136	31	105	77.2%
4	26	14	12	46.2%
<b>Overall</b>	<b>1108</b>	<b>215</b>	<b>893</b>	<b>80.6%</b>

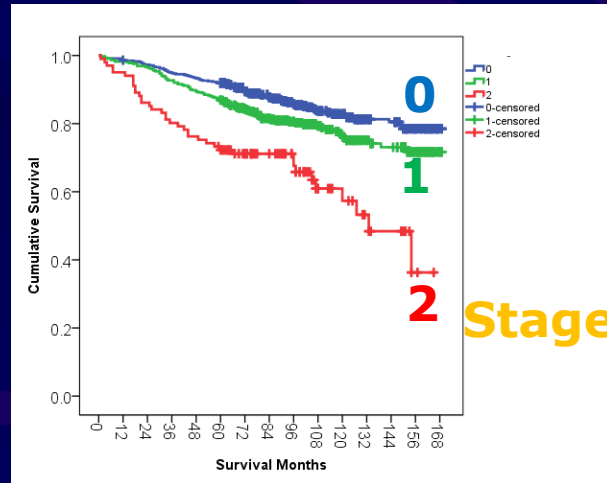
# Kaplan Meier curve, OS ER+Grade+Stage Scoring system



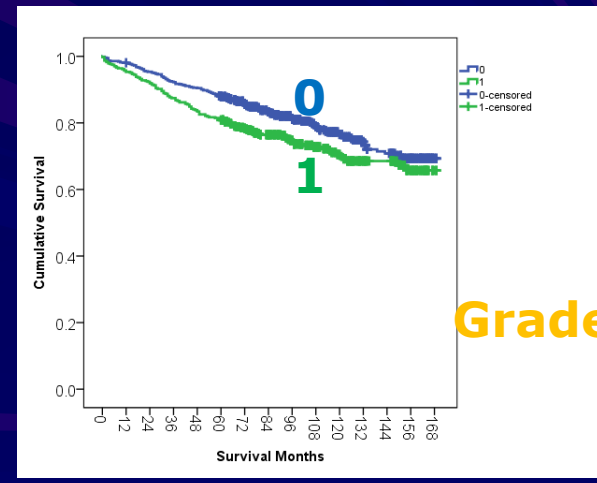
	Total (N)	Dead (N)	Alive (N)	% Survival
<b>ER</b>				
0	936	216	720	76.9%
1	284	69	215	75.7%
<b>Grade</b>				
0	775	164	611	78.8%
1	470	127	343	73%
<b>Stage</b>				
0	584	90	494	84.6%
1	452	96	356	78.8%
2	101	38	63	62.4%



$p=0.63$



$p<0.001$



$p=0.008$

# Summary for ER + Grade + Stage

- Final score (p=.014)
  - Patients with the highest score (score 4) are 8.53x more likely to die than score 0 (95% CI 1.54-47.26)
- Cox regression: ER, Grade and Stage:  
***only stage predicts for survival***
  - Stage score 1 – HR 1.39 (95% CI 1.03 – 1.87)
  - Stage score 2 – HR 3.06 (95% CI 2.07 – 4.52)

# Summary of Results

- **TNM stage and age are predictive of OS**
- **Adding TNP to TNM staging is predictive of OS only for higher TNM stages (stage III and IV) but had no significant effect on TNM stages I and II**
- **The St. Gallen ER/PR/HER2 grouping had no significant impact on survival regardless of TNM stage or age**
- **ER alone and in combination with grade have no significant impact on survival; Stage is the only predictor of survival in this model**



# Conclusions

- Our data **support** the traditional, current TNM staging as a continued relevant predictive tool for breast cancer outcomes
- Our results also suggest that biomarkers are relevant predictors of outcomes, but they primarily improve the accuracy of TNM staging in ***more advanced stages*** of breast cancer
- In early stage breast cancer (Stage I and Stage II) the ER/PR/HER2 status had no significant impact on survival outcomes





# Conclusions

We propose that systematic analysis addressing issues such as:

- 1) Classification system(s) used for determining the ER/PR/HER2 subtypes
- 2) Characteristics of populations studied (Caucasians, minorities, etc.)
- 3) Consistency in choosing the time periods in which studies are conducted

should be performed perhaps both nationally and internationally before biomarkers are fully incorporated into the TNM staging system (bTNM).



# Collaborators

## ■ Surgical Oncology

- John Bell, MD, Professor of Surgery, Director of UTMCK Cancer Institute
- James McLoughlin, MD, Associate Professor of Surgery

## ■ Oncology

- Timothy Panella, MD, Associate Professor of Oncology

## ■ Graduate School of Medicine

- Robert E Heidel, PhD, Statistician

## ■ Pathology

- Jason Chen, MD, Pathology Resident

## ■ Pathology – Outside Learners Program

- Avanti Rangnekar and Prathmesh Desai, Farragut High School and Dept. of Pathology Collaborative Science-Research Program
- Christina Geddam MD, Research Volunteer
- Megan McNeil, Parks Scholar, North Carolina State University



# References

1. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A editors. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010.
2. Bagaria, S et al: Personalizing breast cancer staging by the inclusion of ER, PR, and HER2. *JAMA Surg.* 2014; 149(2):125-9
3. Veronesi, U et al: Rethink TNM: A breast cancer classification to guide to treatment and facilitate research. *The Breast Journal* 2009;15:291-5
4. Jeruss, J et al: Combined use of clinical and pathologic staging variables to define outcomes for breast cancer patients treated with neoadjuvant therapy. *J Clin Oncol.* 2011;29:4654-61
5. Ferguson, NL et al: Prognostic value of breast cancer subtypes, Ki-67 proliferation index, age, and pathologic tumor characteristics on breast cancer survival in caucasian women. *The Breast Journal.* 2013;19:22-30
6. Goldhirsch A, et al. Strategies for subtypes-dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the primary therapy of early breast cancer 2011. *Ann Oncol* 2011 Aug;22(8):1736-1747.
7. Orucevic A, et al. Is the TNM staging system for breast cancer still relevant in the era of biomarkers and emerging personalized medicine for breast cancer – an institution’s 10 year experience . *The Breast Journal.* 2015; 21(2):147-154.
8. Yi, M et al. Novel staging system for predicting disease-specific survival in patients with breast cancer treated with surgery as the first intervention: time to modify the current American Joint Committee on Cancer Staging system. *J Clin Oncol.* 2011; 29(35):4654-4661



Thank you 😊

