

Staging of Differentiated Thyroid Cancer:

TNM, or what else?

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What is „Staging“



- Estimation of „risk“:
 - *Primary outcome: Tumour-related death*
 - *Secondary outcomes: Recurrence, treatment success/failure, etc.*
- „Categorizing“ the individual patient: dividing a population in a limited number of groups with comparable „risk“
- „Categorizing“ the individual patient: determine treatment
- Better name: „Prognostic scoring systems“



Staging systems: requirements



- Stratify a patient according to risk as accurately as possible
- Easy to apply, preferably not use high-tech / expensive / observer dependant parameters
- Universally accepted facilitates comparison of populations and exchange of information



Staging systems for thyroid carcinoma



- To date ca. 15 in literature with death as end-point:
 - *Mostly developed on the population of one hospital*
 - *Several empirically designed (TNM, NTCCTS)*
 - *Not all developed/validated for DTC; some just for PTC*
- Hannequin et al. (Cancer, 1986): same methodology produces different staging systems in different populations
- Different populations, different risk-factors?
 - *E.g. Cady et al: Males higher risk, but Noguchi et al: Females higher risk*
- Additional staging systems developed for recurrence
 - *(e.g. Welsh et al, Nuklearmedizin 2007)*



Comparison of staging systems



- 7 Staging systems developed / validated for DTC
 - AMES: 2 stages; pathology + age +sex
 - Clinical Class: 4 stages; pathology
 - Memorial Sloan-Kettering: 3 stages; pathology + age
 - Ohio State University: 4 stages; pathology
 - TNM (all versions): 4 stages; pathology + age
 - University of Alabama: 3 stages; pathology + age
 - University of Münster: 2 stages; pathology



How to compare staging systems



- NO CONSENSUS!!!!
- Different methodologies in literature (Passler et al, 2003; Brierley et al., 1999)
- Often used: Proportion of Variance Explained
Many methods for calculating!



How we compared staging systems



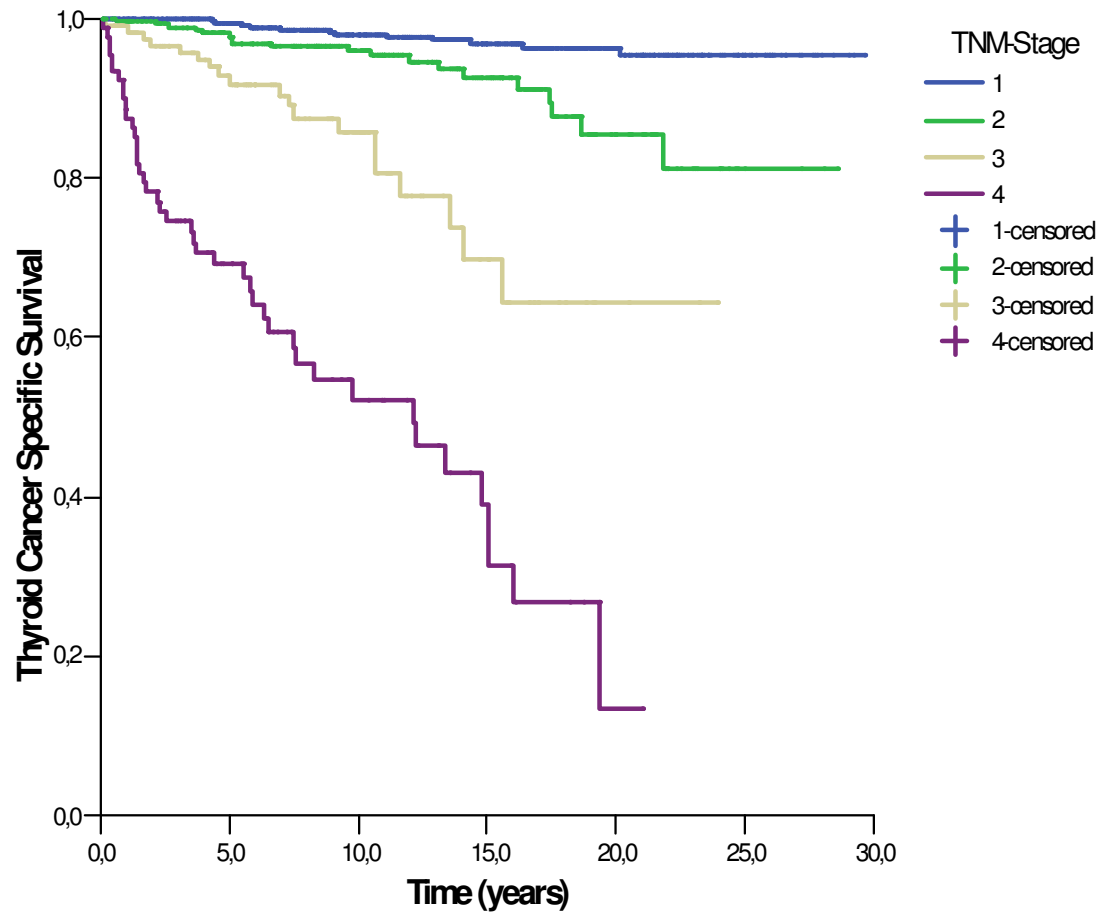
- PVE (method: Schemper M. Statistics in Medicine, 2003)
- Kaplan-Meier with Log-rank test
- Multivariate Cox-regression

- End-point: Thyroid-cancer specific death

- N = 1225 (856 F, 369 M, mean age 47.8 (5-87) y. 875 PTC, 350 FTC), treated in the UKW between 1978 and 2002. Followup 13282 patient-years
- TNM version 5, as 6 could not be applied on all patients with available data



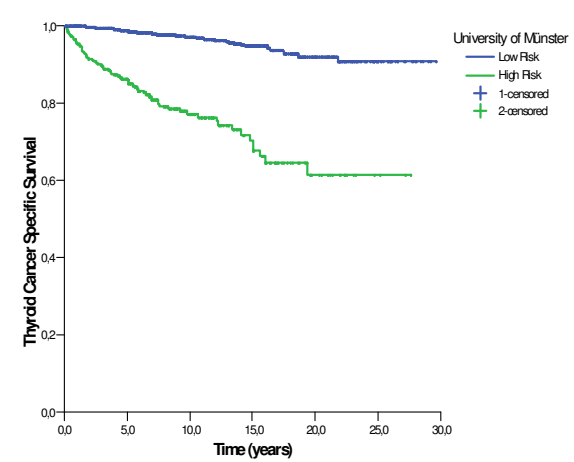
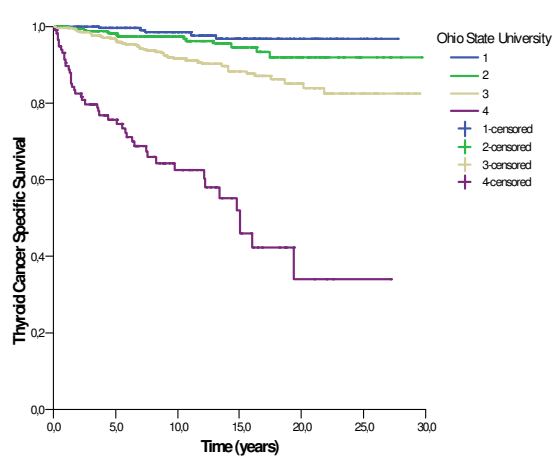
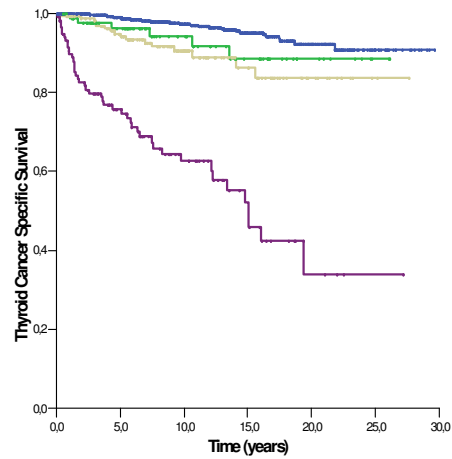
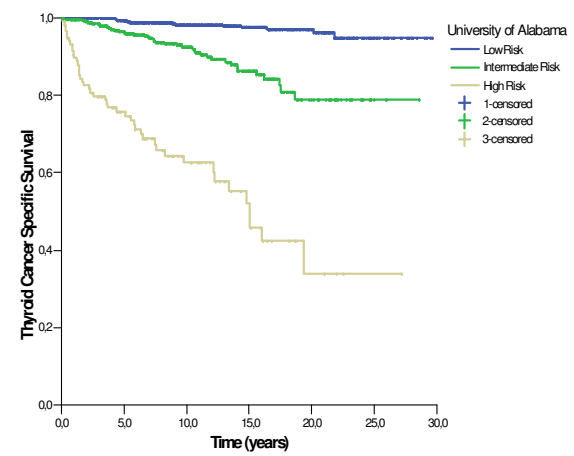
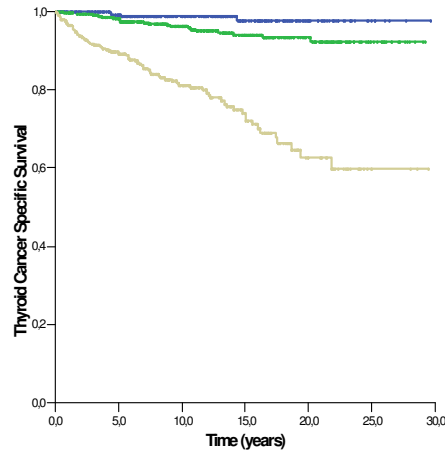
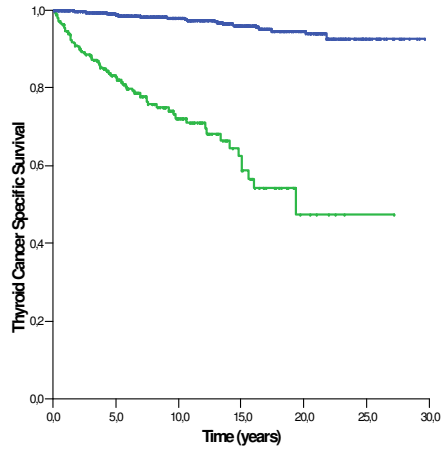
Kaplan-Meier



System	Chi ²
<i>AMES</i>	195.22
<i>Clinical Class</i>	223.47
<i>MSK</i>	114.47
<i>OSU</i>	214.03
<i>TNM</i>	366.02
<i>UAB</i>	248.13
<i>Uni Münster</i>	126.88



Kaplan-Meier



- Multivariate Cox-regression, staging systems as variables, forward selection:
 - *TNM first included in the model ($p < 0.001$); AMES system added in second step ($p = 0.04$)*

- PVE:
 - AMES 0,149
 - Clinical Class 0,143
 - MSK 0,106
 - Ohio State University 0,154
 - TNM 0,225
 - University of Alabama 0,172
 - University of Münster 0,085



- TNM „best“ staging system:
 - *Has the greatest average distance between survival curves*
 - *Almost all other systems redundant in multivariate analysis*
 - *Explains most variance*
 - *Performs no worse than other systems when compared on different patient populations (see Brierley, Passler)*
 - *Generally accepted?*



- Which TNM system?
 - *TNM version 5 vs. 6 differences: T1 <1 cm vs. <2 cm; extrathyroidal invasion T4 vs. T3/T4*
 - *Changes not universally accepted (e.g. DGN recommends recording TNM 5 and 6 simultaneously)*
 - *Further research indicated; possibly TNM-revision?*
 - *At least record the latest (= given standard) version*
 - *Recording other versions optional, but good for backward comparison (both internally and with literature)*



Or what else?



- Develop (and validate!) your own prognostic scoring system:
 - *Results in comparison will likely be better than TNM*
 - *Results and accuracy depend on what is put in*
 - *Results and accuracy depend on the method used*
 - *No consensus on how to develop/validate such a system*
 - *For others (i.e. other hospitals) at best largely of academic interest*
 - *Not usable for comparing with other hospitals (i.e. internal use only)*
 - *Still record TNM for external comparison & possible publications*



Or what else?



- Find out which existing system is best for your hospital
 - *Results most likely worse in own hospital than in the one where the system was developed*
 - *Results and accuracy depend on the method used*
 - *No consensus on how to compare staging systems*
 - *Often not all required data are easily available*
 - *Still record TNM for external comparison & possible publications*



- Prognosis may depend on mutation involved:
- In PTC:
 - *BRAF V600E* mutation more often associated with aggressive disease
 - *RET/PTC1* never found in anaplastic carcinoma
- In FTC:
 - *PAX8-PPARgamma* rearrangement: more aggressive disease than *RAS*
- Further de-differentiation:
 - *P53* mutation strongly associated with de-differentiation; aggressive disease.



Future outlook



- Staging may be indicated by changes in mRNA expression:
- Invasive PTC overexpresses TGF-beta, NFkB, Vimentin
- PTC lymph node metastases: lowered expression of P27kip
- Possibly future staging based on FNAB analysis of Mutations involved and mRNA expression profiles.



Take Home Message(s)



- Staging systems are meant for risk-evaluation, treatment adjustment and comparison of data
- Of the many staging systems for DTC, TNM at least performs no worse than others, possibly even better.
- TNM is easy to apply and generally accepted (but WHICH TNM? At least record the most recent one!)
- The future of prognosis lies in genetic and genomic analysis

