Oncospace™

EXPERIENCE BUILDING A LEARNING HEALTH SYSTEM AND DECISION SUPPORT IN RADIATION ONCOLOGY

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JOHNS HOPKINS MEDICINE

Disclosures

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Elekta Oncology Systems
Toshiba Medical Systems

as well as

Commonwealth Foundation
Maritz Foundation

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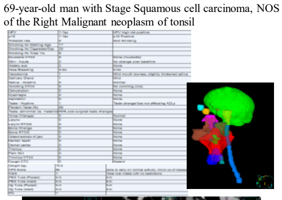
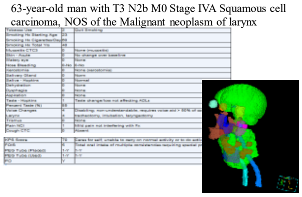
Which patient will do better?

69-year-old man with Stage Squamous cell carcinoma, NOS of the Right Malignant neoplasm of tonsil



63-year-old man with T3 N2b M0 Stage IVA Squamous cell carcinoma, NOS of the Malignant neoplasm of larynx



Types of Clinical Data

- Clinician Assessments
- Patient Reported
  - Quality of life
  - Toxicity and complications
- Biospecimen
  - Labs
  - Pathology
- Image derived features (Radiomics)
- Treatment
  - Radiation Dosimetry
  - Surgery
  - Chemotherapy
- Symptom management
  - Nutritional support
  - Pain medications

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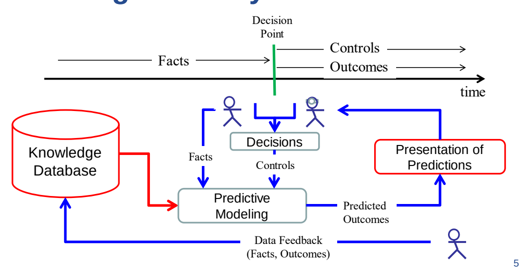
Learning health system



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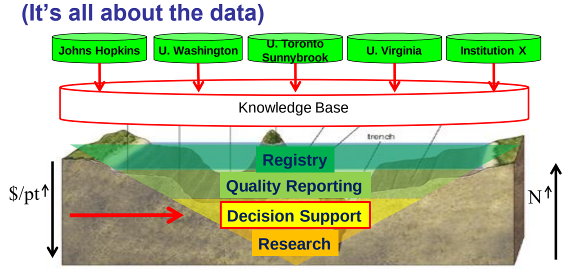
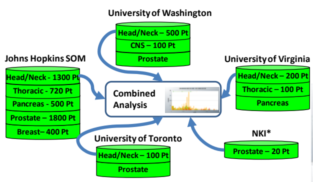
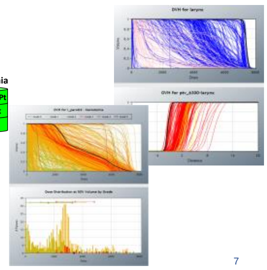
Oncospace Consortium Repository (It's all about the data)



Consortium Status

Michael Bowers MS





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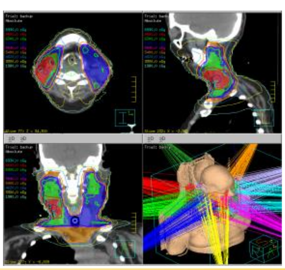
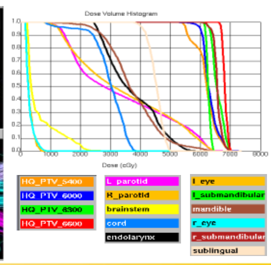
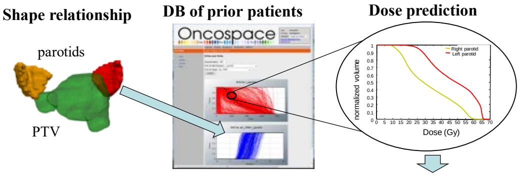
Precision Radiotherapy Treatment





Shape-dose relationship for radiation plan quality



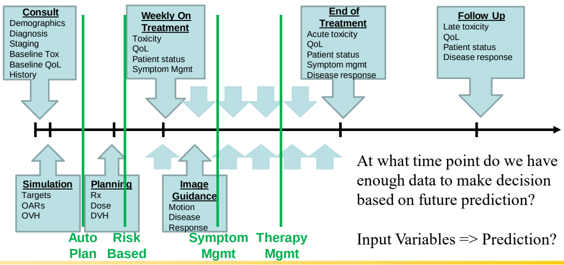
For a selected Organ at Risk and %V, find the lowest dose achieved from all patients whose %V is closer to the selected target volume?

Decisions:

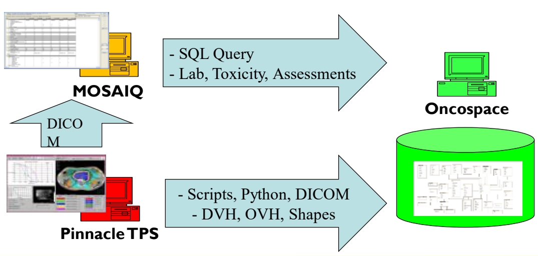
- Plan quality assessment
- Automated planning
  - IMRT objective selection
- Dosimetric trade-offs

Promote Culture of Data Collection

Data collected over entire treatment

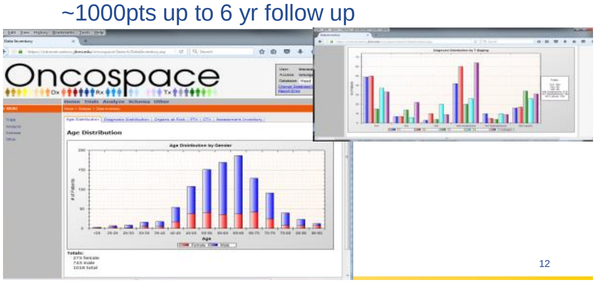


Extract, Transform, Load



Head and Neck Inventory

~1000pts up to 6 yr follow up



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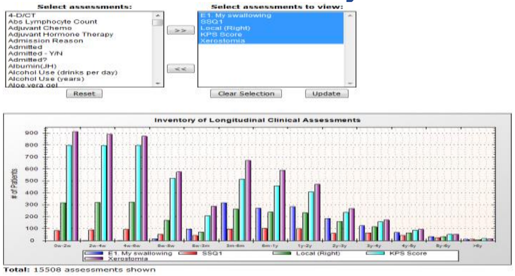
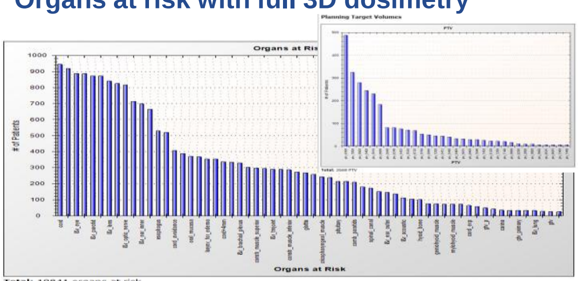
Head and Neck Inventory

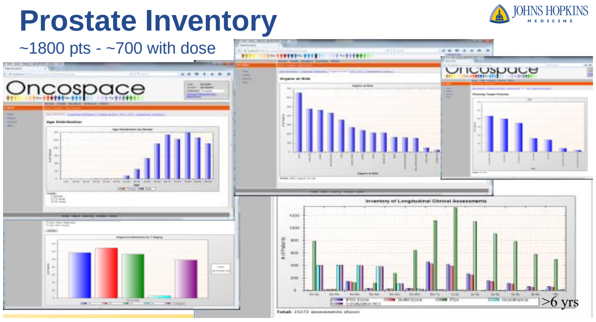


Organs at risk with full 3D dosimetry



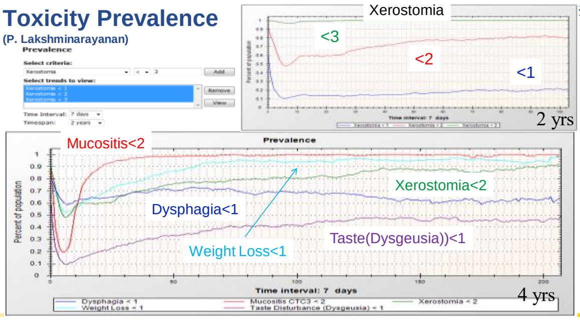
Prostate Inventory

~1800 pts - ~700 with dose

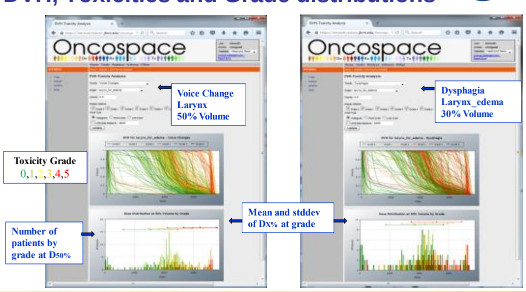


Toxicity Prevalence

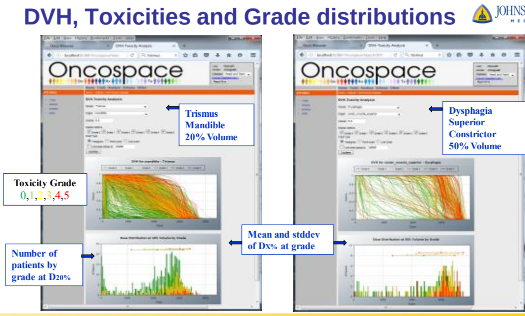
(P. Lakshminarayanan)



DVH, Toxicities and Grade distributions

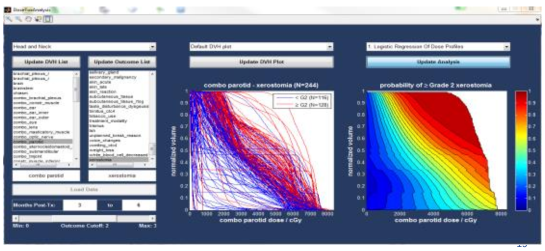


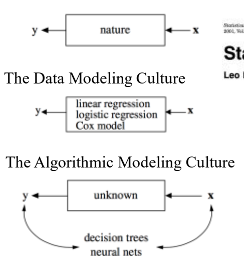
DVH, Toxicities and Grade distributions



Toxicity and Dose Volume Histogram

(Scott Robertson et al…)





Statistical Science
2001, Vol. 16, No. 3, 199–231

Statistical Modeling: The Two Cultures

Leo Breiman

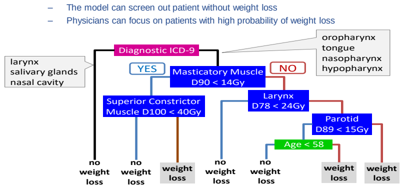
Abstract. There are two cultures in the use of statistical modeling to reach conclusions from data. One assumes that the data are generated by a given stochastic data model. The other uses algorithmic models and treats the data mechanism as unknown. The statistical community has been committed to the almost exclusive use of data models. This commitment has led to irrelevant theory, questionable conclusions, and has kept statisticians from working on a large range of interesting current problems. Algorithmic modeling, both in theory and practice, has developed rapidly in fields outside statistics. It can be used both on large complex data sets and as a more accurate and informative alternative to data modeling on smaller data sets. If our goal as a field is to use data to solve problems, then we need to move away from exclusive dependence on data models and adopt a more diverse set of tools.

Results: Weight loss prediction at planning

Endpoint: > 5kg loss at 3 months post RT

- Predictors:
  - **(1: Diagnosis)** ICD-9 code
  - **(2: Dosimetry)** dose to swallowing muscles, larynx, parotid
  - **(3: Patient)** age
- Prediction result: High negative predictive value
  - The model can screen out patient without weight loss
  - Physicians can focus on patients with high probability of weight loss

Sierra Zhi Cheng MD MS
Minoru Nakatsagawa PhD



Prediction result

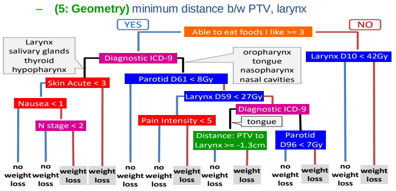
AUC	0.773
Sensitivity	0.766
PPV	0.426
NPV	0.901

Results: Weight loss prediction during RT

Endpoint: > 5kg loss at 3 months post RT

Sierra Zhi Cheng MD MS
Minoru Nakatsagawa PhD

- Predictors:
  - (1: QOL) patient reported oral intake
  - (2: Diagnosis and staging) ICD-9, N stage
  - (3: Dosimetry) dose to larynx, parotid
  - (4: Toxicity) skin toxicity, nausea, pain
  - (5: Geometry) minimum distance b/w PTV, larynx



Prediction result

AUC	0.821
Sensitivity	0.977
PPV	0.462
NPV	0.986

Results of Decision Support for Weight Loss

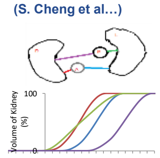
Included radiomic features of the parotid glands

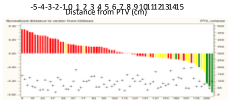
Table 2. Comparison of parameters among CDSS model alone, MD alone, MD+CDSS.

	Sensitivity	Specificity	PPV	NPV	FP	FN	Accuracy	Kappa
CDSS alone	78.3	62.5	75.8	65.8	24.2	34.2	72.0	0.42(0.23, 0.59)
MD alone	68.8	41.9	64.0	47.2	36.1	52.8	58.0	0.11(0.01, 0.21)
Dr. A	21.7	85.0	68.4	42.0	31.6	58.0	47.0	0.07(-0.07, 0.19)
Dr. B	63.3	57.5	69.1	51.1	30.9	48.9	61.0	0.20(0.01, 0.40)
Dr. C	91.7	20.0	63.2	61.5	36.8	38.5	63.0	0.13(-0.03, 0.29)
Dr. D	98.3	5.0	60.8	66.7	39.2	33.3	61.0	0.04(-0.05, 0.13)
MD + CDSS	83.8	30.6	64.4	55.7	35.6	44.3	62.5	0.16(0.06, 0.25)
Dr. A	55.0	62.5	68.8	48.1	31.3	51.9	58.0	0.17(-0.02, 0.35)
Dr. B	81.7	57.5	74.2	67.7	25.8	32.4	72.0	0.40(0.22, 0.59)
Dr. C	98.3	0	59.6	0	40.4	100	59.0	-0.02(-0.06, 0.02)
Dr. D	100.0	2.5	60.6	100	39.4	0	61.0	0.03(-0.03, 0.09)

Pancreas Resectability

(S. Cheng et al…)





Variable, mean	LA (n=76)	BR (n=20)	P-value
Distantce_SMA_0%	-0.8302	-0.3216	0.0764
Distantce_SMA_25%	-0.3739	0.1231	0.0922
Distance_SMA_50%	-0.0362	0.4849	0.0882
Distance_SMA_75%	0.4101	0.9975	0.0805
Distance_ClosestVessel_0%	-1.0421	-0.4121	0.0361*
Distance_ClosestVessel_25%	-0.6513	-0.0427	0.0454*
Distance_ClosestVessel_50%	-0.3894	0.2739	0.0373*
Distance_ClosestVessel_75%	-0.08	0.5603	0.0238*
PTV volume	89.2791	66.7585	0.0065*

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Xerostomia results *Study population*

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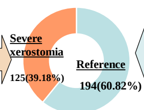
N = 319
Age (mean ± sd) = 57.82 ± 11.10
Male: 76.8%
Caucasian: 75.69%
Tobacco use history: 56.84%
Alcohol use history: 49.32%

Chemotherapy: 61.34%
HPV: 57.89%
Weight loss: 9.23 ± 7.42
Parotid D95: 10.88 ± 6.33
Submandibular D70: 55.72 ± 12.80



Chemotherapy: 80%
HPV: 78.57%
Weight loss: 5.36 ± 5.87
Parotid D95: 6.6 ± 5.03
Submandibular D70: 41.94 ± 23.59

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Xerostomia Prediction (3-6 Months post RT)

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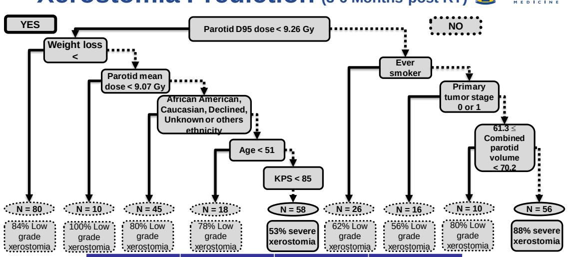

AUC	Accuracy	Sensitivity	Specificity
0.627	0.687	0.536	0.784

Xuan Hui MD MS

Results

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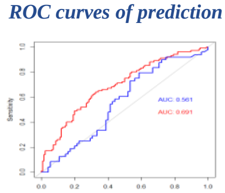
ROC curves of prediction using parotid D95 and parotid mean dose



- CART with10-fold cross-validation to compare prediction power using parotid D95 and parotid mean dose
- AUC(parotid D95) = 0.691
- AUC(parotid mean dose) = 0.561

	AUC	Accuracy*	Sensitivity	Specificity
Parotid D95	0.691	0.659	0.640	0.674
Parotid mean dose	0.561	0.561	0.792	0.413

*Accuracy: the weighted average of a test's sensitivity and specificity

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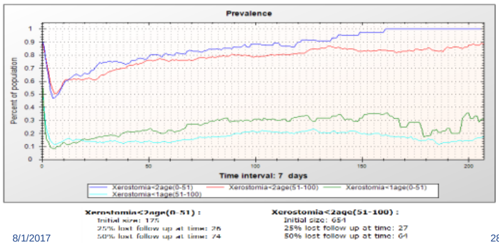
Xerostomia prevalence
separated by age = 51



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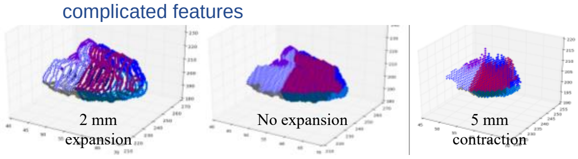
Parametric Shape-Based Features

What are they?
- **Consistently identifiable substructures** that characterize a region of interest
- Based on **geometric image manipulation**

How are they calculated?
- Regions of interest are **normalized** to a common atlas anatomy
- Features are calculated based on **predefined parameters,** such as expansion/contraction, slicing, etc.

Defining a Feature

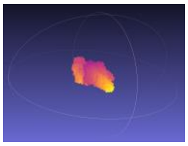
- Transformations can be composed to create more complicated features



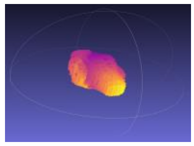
Shells+Octants Feature: Defined by expansion, contraction, and partitioning into octants about the origin.
Shown here applied to a parotid gland.

Compute Dose to a Feature

- Dose distribution can be mapped onto each sub-structure



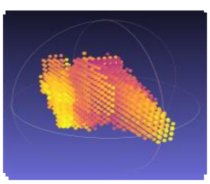
Visualization of a parotid gland with dose mapping



Shell created from surface of parotid to 2mm expansion with dose mapping

Compute Dose to a Feature

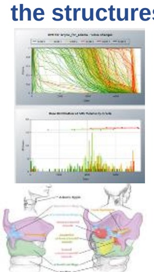
- Dose distribution can be mapped onto each sub-structure

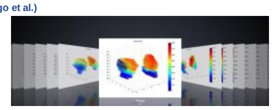


Shown here, a visualization of the dose mapped onto each octant of a parotid gland.

Color map is relative to each subsection

Spatially dependent features of dose in the structures (F. Marungo et al.)





Method	Voice dysfunction $n=99$, $n_+=8$, $n_-=91$	Xerostomia $n=364$, $n_+=275$, $n_-=89$
Bagged Naïve Bayes (1000 iterations)	0.915	0.743
Bagged Linear Regression (1000 iterations)	0.905	0.737
Naïve Bayes	0.900	0.734
Linear Regression	0.896	0.731
Random Forest (1000 trees)	0.724	0.683
$NTCP_{LKB}$	0.596	0.700

Needs…

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- For the vision of a learning health system, significantly improved user interfaces are required
- In order to present a prediction, we must first present the "quantitative" patient state
- More continuous assessment of patient condition is needed through mobile devices
- Stronger linkages between genomic, pathology and clinical databases

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Summary

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- We can quantify the patient experience and are improving our capabilities rapidly
- It is possible to collect and house RT data/knowledge in a clinical setting
- Current shape-based auto-planning utilizes a learning health system
- Data science models are maturing that can convert the knowledge to clinical predictions
- Sharing data across institutions allows for experience **and expertise** sharing

…we have work to do which requires real partnerships between clinicians and informaticists

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- **Toshiba**
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  - John Haller
- **Elekta**
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  - Mark Philips PhD
  - Kristi Hendrickson PhD

Xerostomia Prediction

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Study Design

- *Primary outcome*: Xerostomia grade (CTCAE v4.0) at 90 - 150 days after RT
  - Grade 2 & 3 – severe xerostomia
  - Grade 0 & 1 – reference
- *Confounding factors*
  - ***Time-fixed parameters***: age, gender, race, chemotherapy, smoking status, alcohol use, HPV status, tumor stage (T, N, M, overall), Karnofsky Performance Scale (KPS), tumor site, volume of salivary glands, dosimetric factors
  - ***Time-varying parameters***: weight, taste function

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Results

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Backward stepwise elimination

	OR	p-value	95% Confidence Interval
alpha = **0.05**			
Parotid D95	1.15	<0.001	[1.09, 1.21]
Submandibular D70	1.04	<0.001	[1.01, 1.05]
Submandibular D60	1.05	0.036	[1.02, 1.07]
alpha = **0.01**			
Parotid D95	1.15	<0.001	[1.09, 1.21]
Submandibular D70	1.04	<0.001	[1.01, 1.05]

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Results

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Parametric modeling – Univariate Analyses

Parameters	OR	p-value	95% Confidence Interval
Chemotherapy			
No	ref.		
Yes	2.52	**0.001**	[1.49, 4.26]
HPV			
No	ref.		
Yes	2.67	**<0.001**	[1.32, 5.38]
Weight loss at 1st visit			
≤ 5 kg	ref.		
loss > 5 kg	2.58	**<0.001**	[1.62, 4.09]
Parotid D95			
	1.15	**<0.001**	[1.09, 1.21]
Submandibular D70			
	1.04	**<0.001**	[1.02, 1.06]
Parotid mean dose			
	1.04	**0.023**	[1.01, 1.08]

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