UMC Utrecht

Inter- and intra-laboratory variation in grading of invasive breast cancer: a nationwide study of 33,043 patients in the Netherlands

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University Medical Center Utrecht

European Society of Pathology

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Pathology is Nice

7 – 11 September 2019, Nice Acropolis Convention Centre, France

Disclosure Information

I hereby declare that I have no conflict of interest

Breast cancer: background

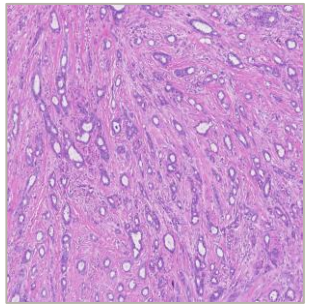
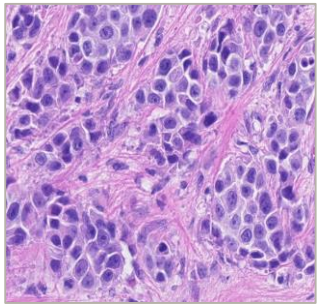
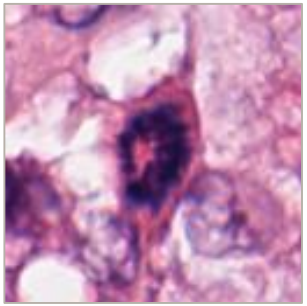
- Most common type of cancer in European women[1]

- Breast cancer management: ***it all starts with pathology***
  - Subtype: **PATHOLOGY**
  - Prognosis: **PATHOLOGY**
  - Treatment: **PATHOLOGY**

1. International Agency for Research on Cancer (WHO), source: GLOBOCON 2018

Breast cancer biomarkers

- **Histologic grade**
  - B&R (modified)

  - **Clinical decisions**
    - Chemotherapy
    - Radiotherapy
    - Gene-expression profiling

Reproducibility histologic grading

- No more than moderate[1-4]

But how are we doing in daily clinical practice?

1. Boiesen et al. *Acta Oncol* 2000: 39(1):41-45
2. Frierson et al. *Am J Clin Pathol* 1995:103(2):195-198
3. Italian Network for Quality Assurance of Tumour Biomarkers (INQAT group). *Pathologica* 2005:97(1):1-6
4. Meyer et al. *Mod Pathol* 2005:18(8):1067-1078

Real-life data on a Dutch nationwide level

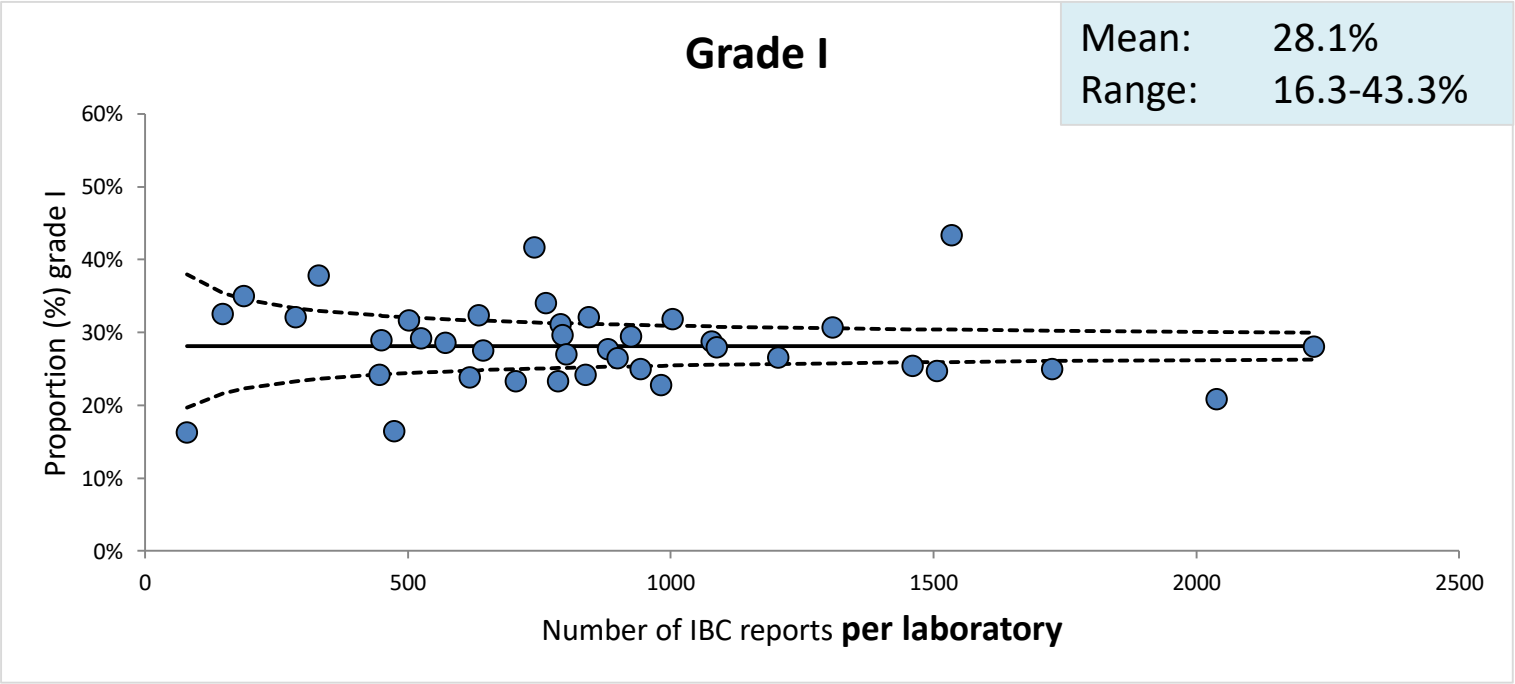
the nationwide network and registry of histo- and cytopathology in the Netherlands

- **Synoptic reporting**

1. Sluijter et al. *Virchows Archiv* 2016:468(4):639-649.
2. PALGA Foundation, *Annual* Report 2018

Grading in the Netherlands; 2013-2016 (n=33,792)

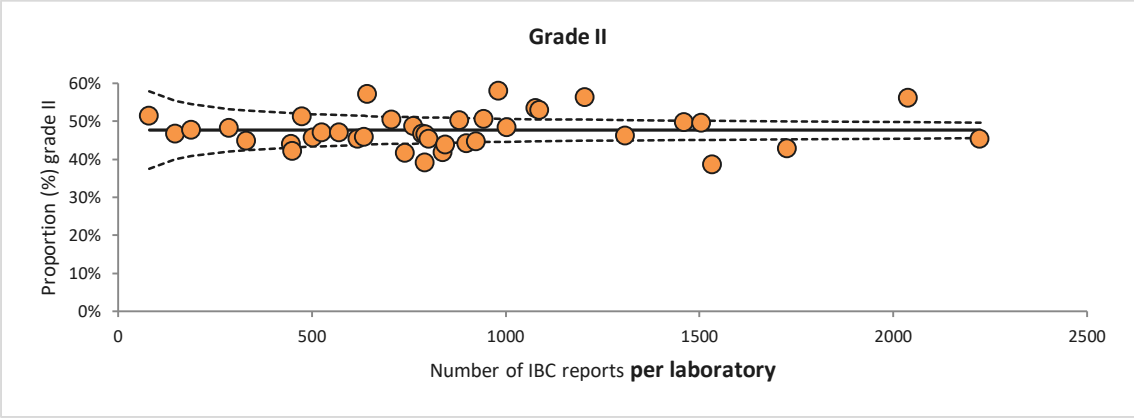
Laboratory-level (n=39)



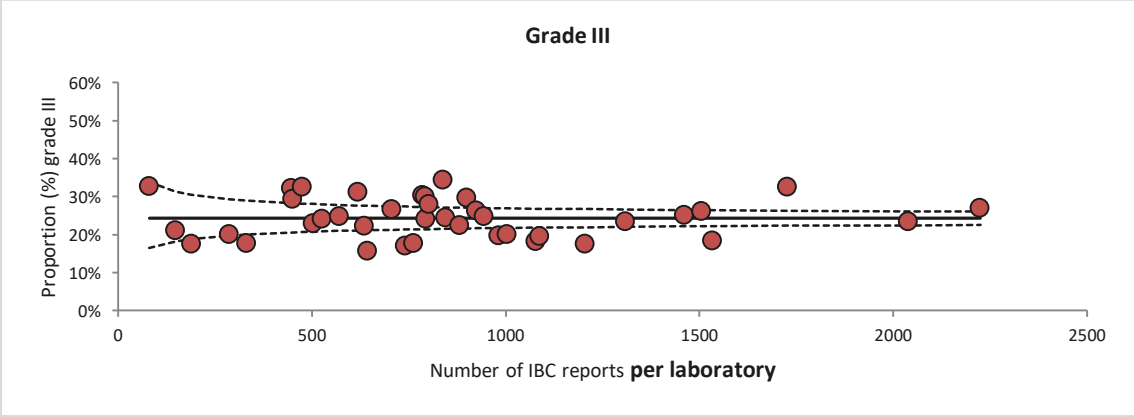
Case-mix: age, tumour size, type of surgery, histologic subtype, ER/PR- and, HER2-receptor status

Grading in the Netherlands; 2013-2016 (n=33,792)

Laboratory-level (n=39)



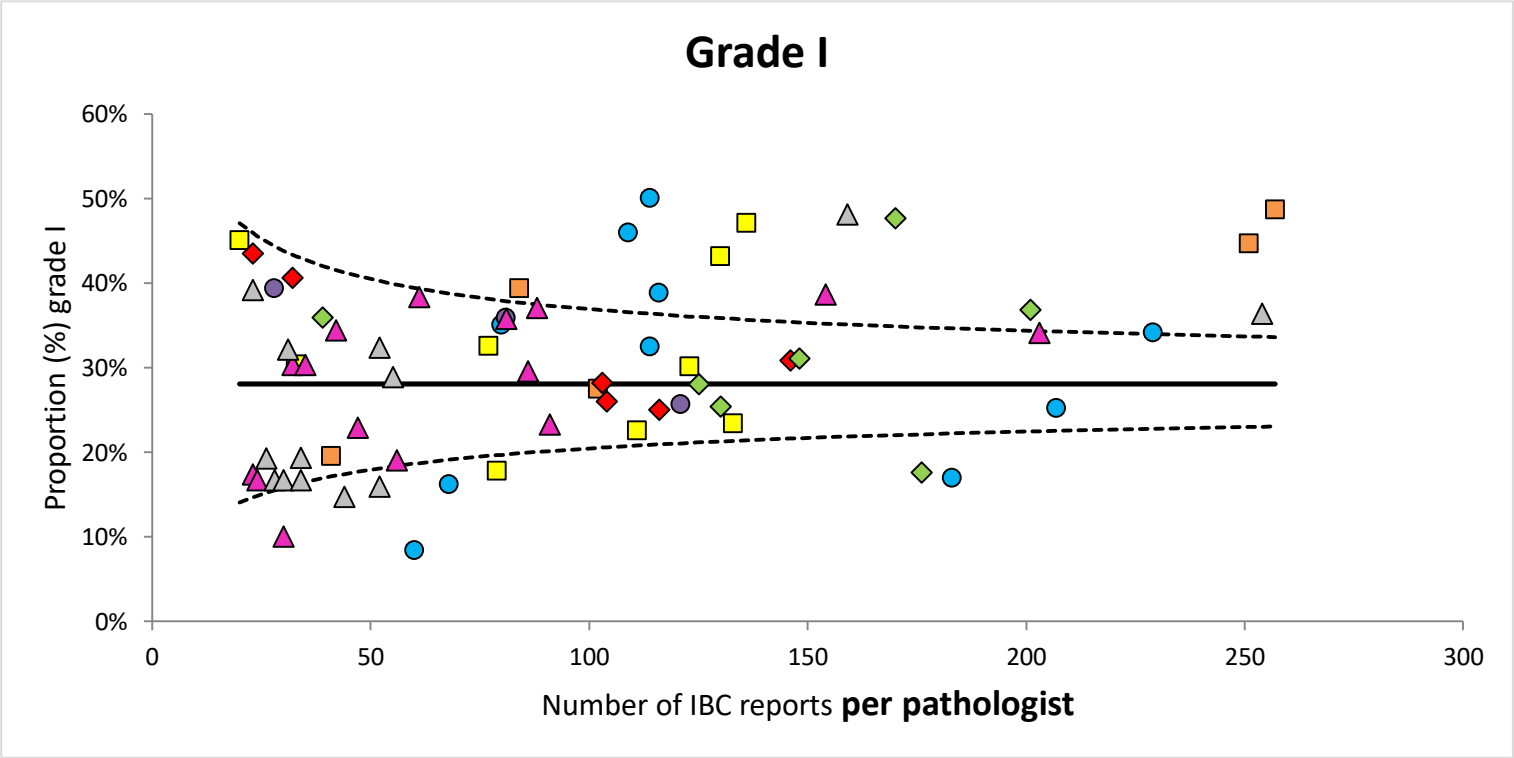
Mean: 47.6%
Range: 38.4-57.8%



Mean: 24.3%
Range: 15.5-34.3%

Grading in the Netherlands; 2013-2016

Pathologist-level (n=68, 8 laboratories)



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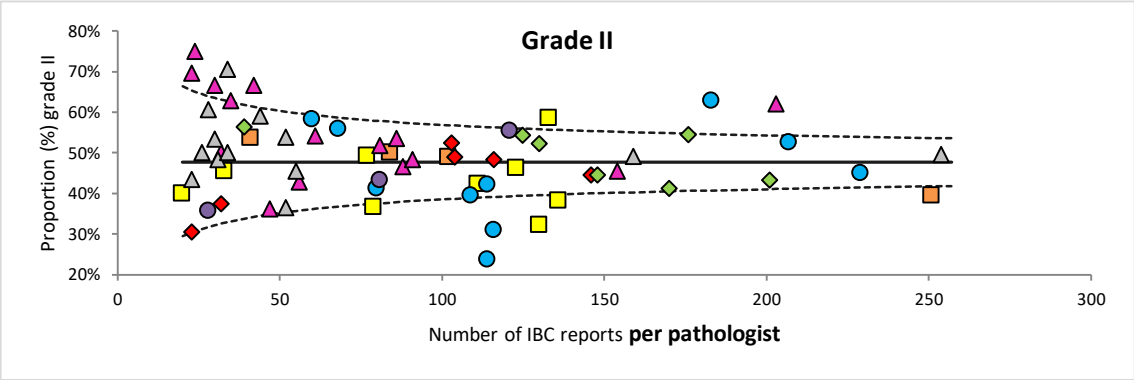

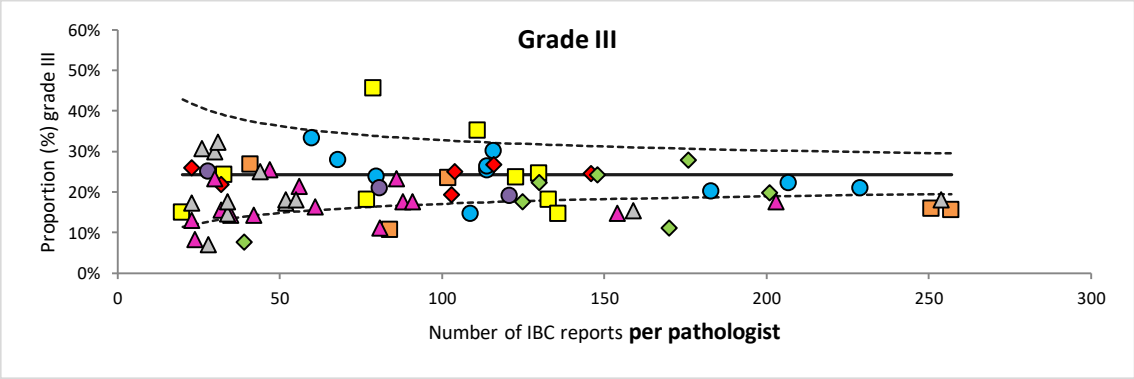

Grading variation; does it really matter?

Chemotherapy (n=19,461)

According to the Dutch breast cancer guideline, adjuvant chemotherapy (aCT)

Invasive breast cancer reports with complete

Table 4. (Neo)-Adjuvant systemic treatment recommendations for ER positive/*HER2* negative early breast cancer

Subtypes according to clinical-pathological and genomic risk assessment	Treatment recommendation	De-escalation	Escalation
	ER positive & HER2-negative		
High receptor, low tumour burden (pT1a, pT1b), no nodal involvement (pN0), low proliferation, low grade or low "genomic risk"	Endocrine therapy alone according to menopausal status		
Premenopausal	Tamoxifen 5 years	No role for extended adjuvant tamoxifen beyond 5 years No OFS	
Postmenopausal	Tamoxifen or AI for 5 years	The majority of the panel recommended against extended adjuvant endocrine therapy beyond 5 years	
High/Intermediate degree of ER and PgR expression, intermediate tumour burden pT1c, pT2, pN0 or pN1 (1-3), intermediate or high proliferation or grade, and/or intermediate "genomic risk"	Endocrine therapy according to menopausal status plus adjuvant chemotherapy		

Curigliano et al. *Ann Oncol* 2017: 28(8):1700-1712

Conclusion: histologic grading

- Synoptic pathology reports of >**33,000 patients**
- **Substantial inter- and intra-laboratory variation** in grading of invasive breast cancer in daily clinical practice
  - Not explained by differences in case-mix
- Biomarker of major clinical importance
  - Indication chemotherapy
    - **1 in 3 breast cancer patients**
    - **1 in 2 lymph-node negative breast cancer patients**
- **Decrease in variation warranted!**
- **Interventions**
  - Feedback reports
  - E-learning

Acknowledgements

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palga

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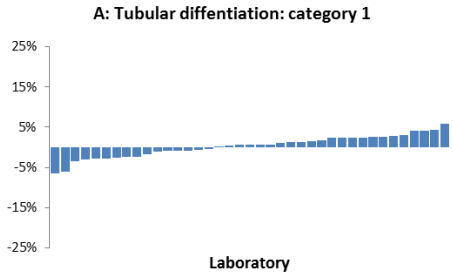
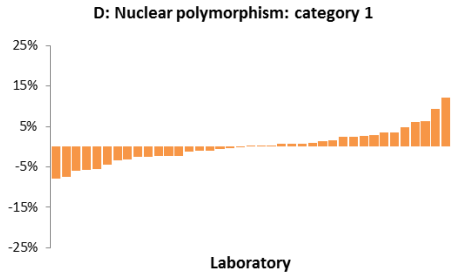
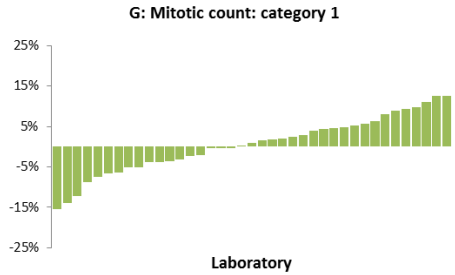
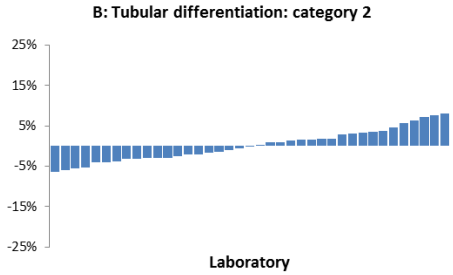
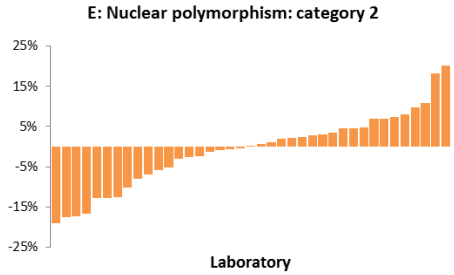
Categories of grading

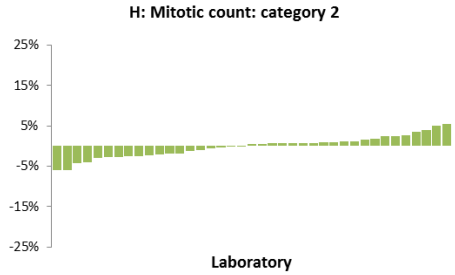


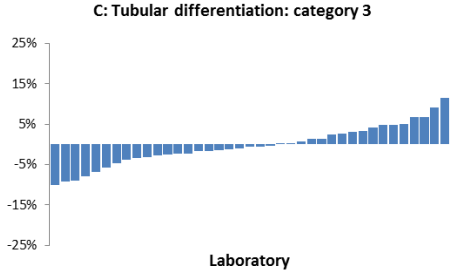


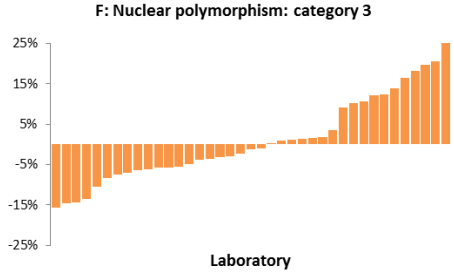


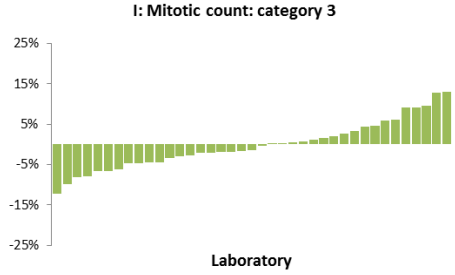






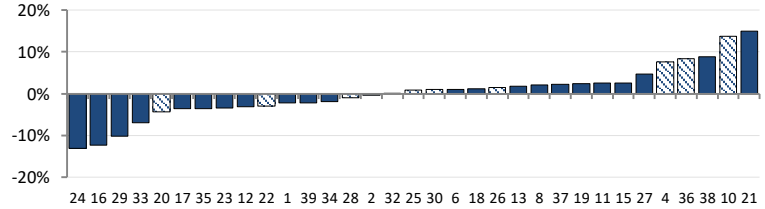




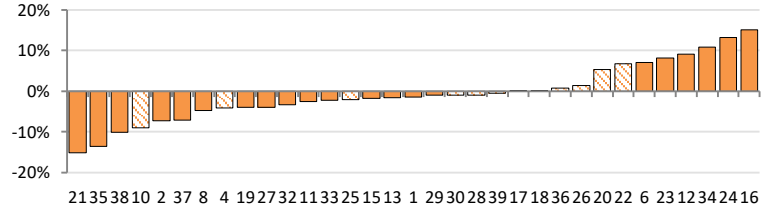


Preliminary results: follow-up of feedback reports

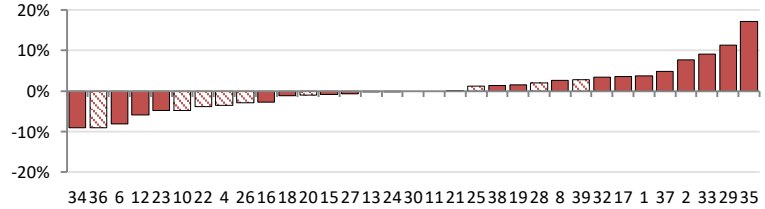
A: Before feedback reports: grade I



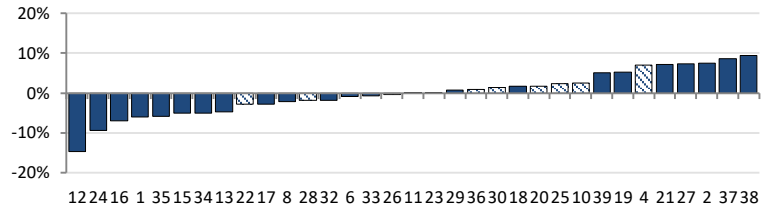
B: Before feedback reports: grade II



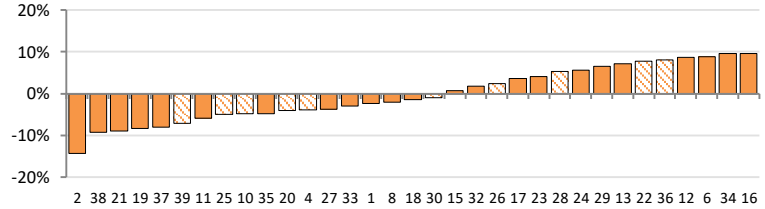
C: Before feedback reports: grade III



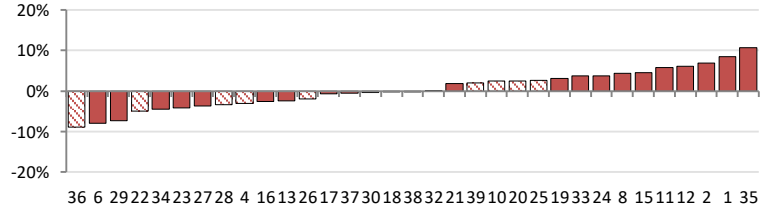
D: After feedback reports: grade I



E: After feedback reports: grade II



F: After feedback reports: grade III



Data selection

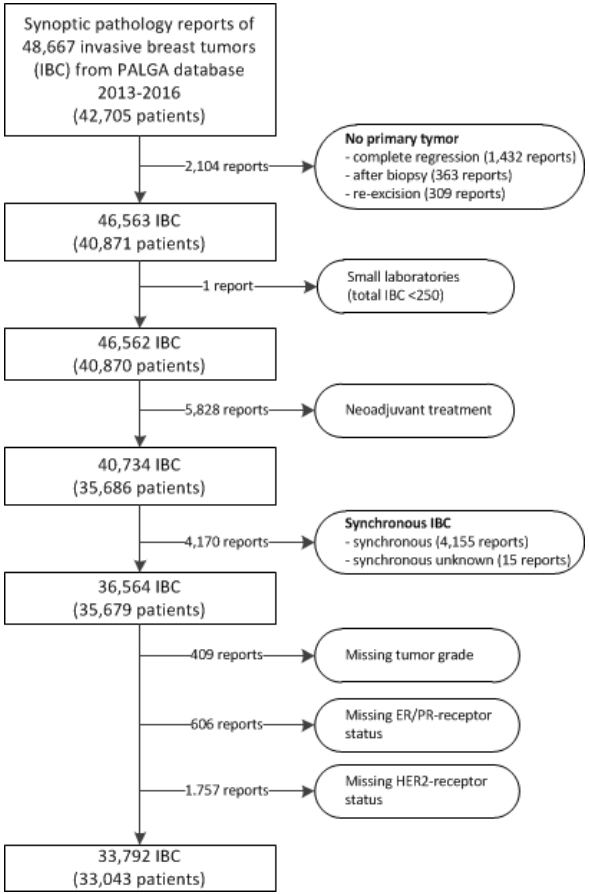


TABLE 1. Characteristics of the 33,792 included invasive breast cancer (IBC) lesions from the PALGA database 2013-2016

	Total (n=35,549)	Grade 1 (n=9,960)	Grade 2 (n=16,906)	Grade 3 (n=8,683)	p-value
Age (y)*	62.2 (12.1)	62.4 (10.8)	62.8 (11.8)	60.7 (13.8)	0.000
Sex, n (%)					
Female	33,537 (99.2%)	9,441 (99.4%)	15,967 (99.2%)	8,129 (99.1%)	0.045
Male	255 (0.8%)	54 (0.6%)	131 (0.8%)	70 (0.9%)	
Tumour size (cm)*	1.9 (1.3)	1.4 (0.9)	1.9 (1.4)	2.3 (1.5)	0.000
Type of surgery, n (%)					
Mastectomy	12,209 (36,1%)	2,548 (26.8%)	6,172 (38.3%)	3,489 (42.6%)	0.000
Breast conserving	21,583 (63.9%)	6,947 (73.2%)	9,926 (61.7%)	4,710 (57.4%)	
Histologic subtype, n (%)					
Ductal	28,547 (84.5%)	8,727 (91.9%)	12,382 (76.9%)	7,438 (90.7%)	0.000
Lobular	4,432 (13.1%)	647 (6.8%)	3,465 (21.5%)	320 (3.9%)	
Other	813 (2.4%)	121 (1.3%)	251 (1.6%)	441 (5.4%)	
ER/PR receptor status, n (%)					
Positive	29,576 (87.5%)	9,373 (98.7%)	15,162 (94.2%)	5,041 (61.5%)	0.000
Negative	4,216 (12.5%)	122 (1.3%)	936 (5.8%)	3,158 (38.5%)	
HER2-receptor status, n (%)					
Positive	3,340 (9.9%)	212 (2.2%)	1,335 (8.3%)	1,793 (21.9%)	0.000
Negative	30,452 (90.1%)	9,283(97.8%)	14,763 (91.7%)	6,406 (78.1%)	

* Mean (SD)

TABLE 2. Scores of the three components of the modified Bloom and Richardson classification and overall score for the 33,972 included invasive breast cancer (IBC) lesions from the PALGA database 2013-2016

Characteristics		Total (n = 33,792)	Grade I (n = 9,495)	Grade II (n = 16,098)	Grade III (n = 8,199)
Tubular differentiation, n (%)					
1	> 75% of cells	3,895 (11.5%)	3,698(38.9%)	197 (1.2%)	0 (0.0%)
2	10-75% of cells	8,724 (25.8%)	4,694 (49.4%)	3,371 (20.9%)	659 (8.0%)
3	<10% of cells	21,173 (62.7%)	1,103 (11.6%)	12,530 (77.8%)	7,540 (92.0%)
Nuclear polymorphism, n (%)					
1	Mild 1*	2,942 (8.7%)	2,818 (29.7%)	124 (0.8%)	0 (0.0%)
2	Moderate 2**	20,741 (61.4%)	6,545 (68.9%)	12,258 (76.1%)	1,938 (23.6%)
3	Severe 3***	10,109 (29.9%)	132 (1.4%)	3,716 (23.1%)	6,261 (76.4%)
Mitotic count, n (%)					
1	< 7 per $2mm^2$	21,164 (62.6%)	9,273 (97.7%)	11,891 (73.9%)	0 (0.0%)
2	≥ 8 ≤12 per $2mm^2$	5,163 (15.3%)	213 (2.2%)	3,270 (20.3%)	1,680 (20.5%)
3	≥ 13 per $2mm^2$	7,465 (22.1%)	9,(0.1%)	937 (5.8%)	6,519 (79.5%)
Total score					
3	grade I	1,127 (3,3%)	1,127 (11.9%)	-	-
4	grade I	2,796 (8.3%)	2,796 (29.5%)	-	-
5	grade I	5,572 (16.5%)	5,572 (58.7%)	-	-
6	grade II	11,127 (32.9%)	-	11,127 (69.1%)	-
7	grade II	4,971 (14.7%)	-	4,971 (30.9%)	-
8	grade III	4,277 (12.7%)	-	-	4,277 (52.2%)
9	grade III	3,922 (11.6%)	-	-	3,922 (47.8%)

* Nuclei small with little increase in size in comparison with normal breast epithelial cells, regular outlines, uniform nuclear chromatin, little variation in size.
** Cells larger than normal with open vesicular nuclei, visible nucleoli, and moderate variability in both size and shape
*** Vesicular nuclei, often with prominent nucleoli, exhibiting marked variation in size and shape, occasionally with very large and bizarre forms

New St. Gallen guideline

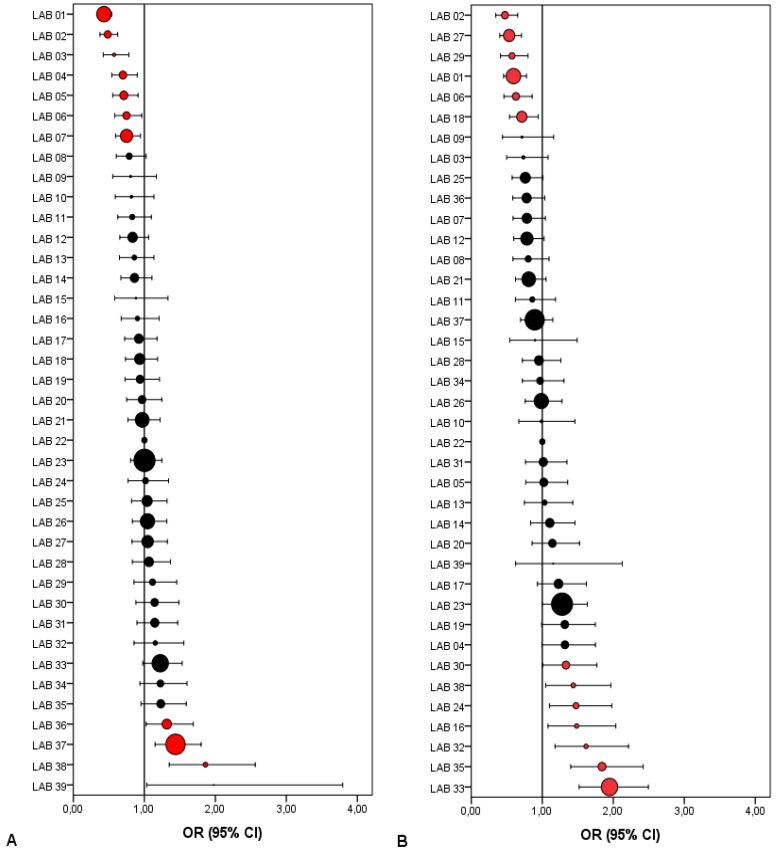
Table 4. Systemic Therapy for ER+ HER2- Breast Cancer

Stage		Ovarian Suppression	Type & Duration of Endocrine Therapy	Chemotherapy
Stage 1	T1ab	No OFS	AI or tam (5yrs)	No
	T1c	No OFS*	AI or tam (5yrs)	Individualized decision based on: T size, N status, histological subtype, LVI, grade, proliferation, quantitative hormone receptor expression, , and preferably, genomic signatures; and patient preferences
Stage 2	Node-negative	OFS and AI/tam for high risk (large T; warranting chemo, Age ≤ 35; high grade; adverse gene signature)	AI preferred as initial therapy; extended favored (especially after initial 5 yrs Tam)	
	Node-positive	OFS and AI/tam	Extended	
Stage 3		OFS and AI/ tam	Extended	Yes

AI = aromatase inhibitor
Tam = tamoxifen
LVI = lymphovascular invasion
OFS = ovarian function suppression
*some consider OFS along same criteria as stage 2, node-negative

Burstein (2019)

Case-mix? Age, tumour size, type of surgery, histologic subtype, ER/PR-receptor status, HER2-receptor status



20 laboratories (51.3%) with at least 1 significantly deviant OR