CORRELATION OF THE RESULTS OF KI67 IN INTRINSIC SUBTYPES OF INVASIVE BREAST CARCINOMAS WITH THE EFFECTS OF SYSTEMIC NEOADJUVANT TREATMENT

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Ki67 - Immunohistochemistry

- Ki-67 is a nuclear proliferation marker expressed in all phases of the cell cycle except G0
- Generally, breast cancers expressing high levels of Ki67 correlates with worse outcomes
- Ki67 level above 20% (St. Gallen 2013), are characteristic for high-risk of poor prognosis
- Ki67 values before starting treatment could help to predict response, while those measured after chemotherapy could help predict disease-free survival

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Molecular subtypes and local-regional control of breast cancer Simona Maria Fragomeni, MD, et. al.

Ki67 in breast pathology

- Intrinsic subtypes (Luminal A/Luminal B (HER2 neg) (since 2011).
- IHC Ki67 after systemic therapy is done routinely in our Dept. since 2017.

New applications

- Preoperative endocrine prognostic index (PEPI)
- $Ki67^{B,}$ $Ki67^{2W}$

Ki67 Preoperative endocrine prognostic index (PEPI)

Outcome Prediction for Estrogen Receptor–Positive Breast Cancer Based on Postneoadjuvant Endocrine Therapy Tumor Characteristics

Matthew J. Ellis, Yu Tao, Jingqin Luo, Roger A'Hern, Dean B. Evans, Ajay S. Bhatnagar, Hilary A. Chaudri Ross, Alexander von Kameke, William R. Miller, Ian Smith, Wolfgang Eiermann, Mitch Dowsett

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Ki67 level		
0-2.7%	0	0
2.8-7.3%	1	1
7.4-19.7%	1	2
19.8-53.1%	2	3
53.2% or more	3	3

Table 1 Post neoadjuvant endocrine therapy residual disease factors comprising the PEPI score* for RFS and BCSS

Factor	RFS risk points	BCSS risk points
Pathologic T stage		
pT0-2	0	0
pT3/4	3	3
Pathologic N stage		
pN0	0	0
pN1-3	3	3
ER Allred score		
0-2	3	3
3-8	0	0
Ki67 level		
0-2.7%	0	0
2.8-7.3%	1	1
7.4-19.7%	1	2
19.8-53.1%	2	3
53.2% or more	3	3

*Determining PEPI score: a patient's PEPI score is determined by summing risk points corresponding to pT stage, pN stage, Ki67 and Allred score from their surgical specimen disease following neo-adjuvant endocrine therapy. For example, a patient with a pT2 pN1 tumor with Ki67 =5% and ER Allred score =5 would be assigned a PEPI score of 4 (0+3+1+0) for both RFS and BCSS. RFS, relapse-free survival; BCSS, breast cancer specific survival.

Aims

- Evaluating changes in Ki67 generated by NAT in Breast Carcinoma with consideration of intrinsic subtypes.
- Introduction more precise Ki67 measurement standards.

Material

The study used 148 breast cancer cases qualified for neoadjuvant treatment. In the evaluated group, there were:

- 14 cases of Luminal A carcinomas,
- 14 cases of Luminal B (HER2 negative) carcinomas,
- 52 cases of Luminal B (HER2 positive) carcinomas,
- 10 cases of HER2 positive (non-luminal) carcinomas,
- 58 cases of triple-negative (ductal) carcinomas.

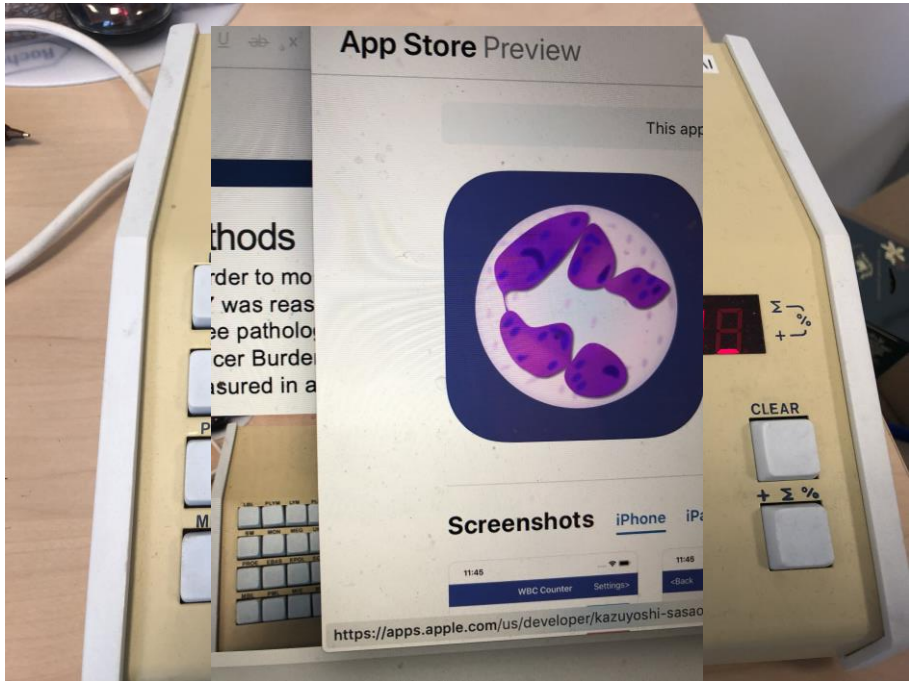
Material cont.

- Clinically all tumors were in Stage II and Stage III , Invasive NST and 10 lLC.
- Tumor size: 1,7 – 6,9 cm
- Grade: G1: 10 cases
- G2: 59 cases
- G3 79 cases
- Metastases in local lymph nodes: 127 cases/148 cases;

- The were no uniform neoadjuvant treatment in study cases (HTh, CHTh , anty-HER2)

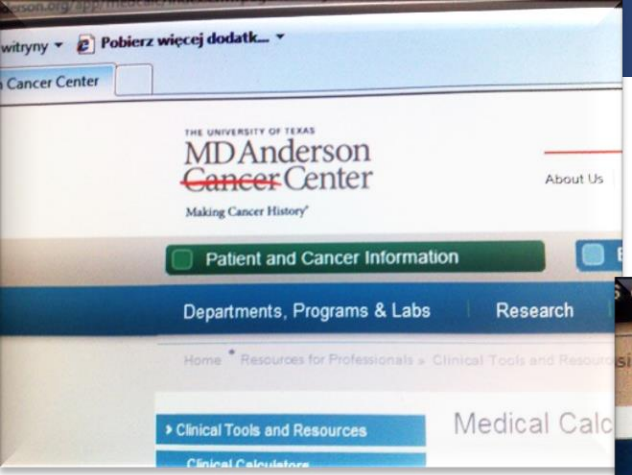
Methods

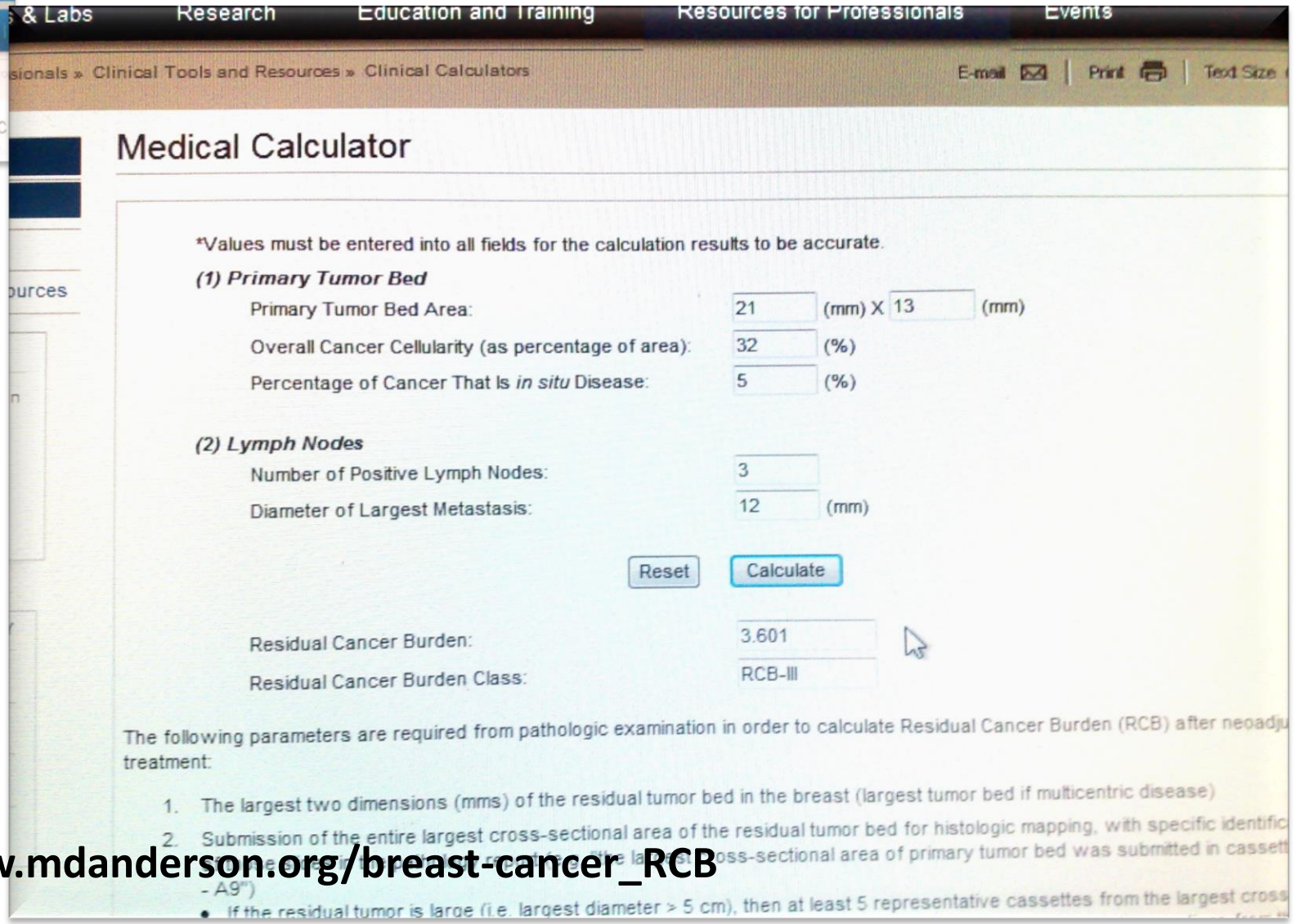
- In order to more accurate measurements than the routine Ki67 evaluation (Ki-67 Antigen (Dako Omnis), Ki67 was reassessed in the CB material. Ki67 was evaluated in 500 cells. Three pathologists carried out an independent assessment of Ki67. Residual Cancer Burden value, percentage of pCR and the decrease in cellularity were measured in all post treatment histologic material.



H16/13318/1	80%	401/500 (80,2%)
H17/9283/1	10%	164/500 (32,8%)
H17/10546	95%	453/500 (90,6%)
H17/10496	90%	364/500 (72,8%)
H17/13946	80%	381/500 (76,2%)

Residual cancer burden (RCB)



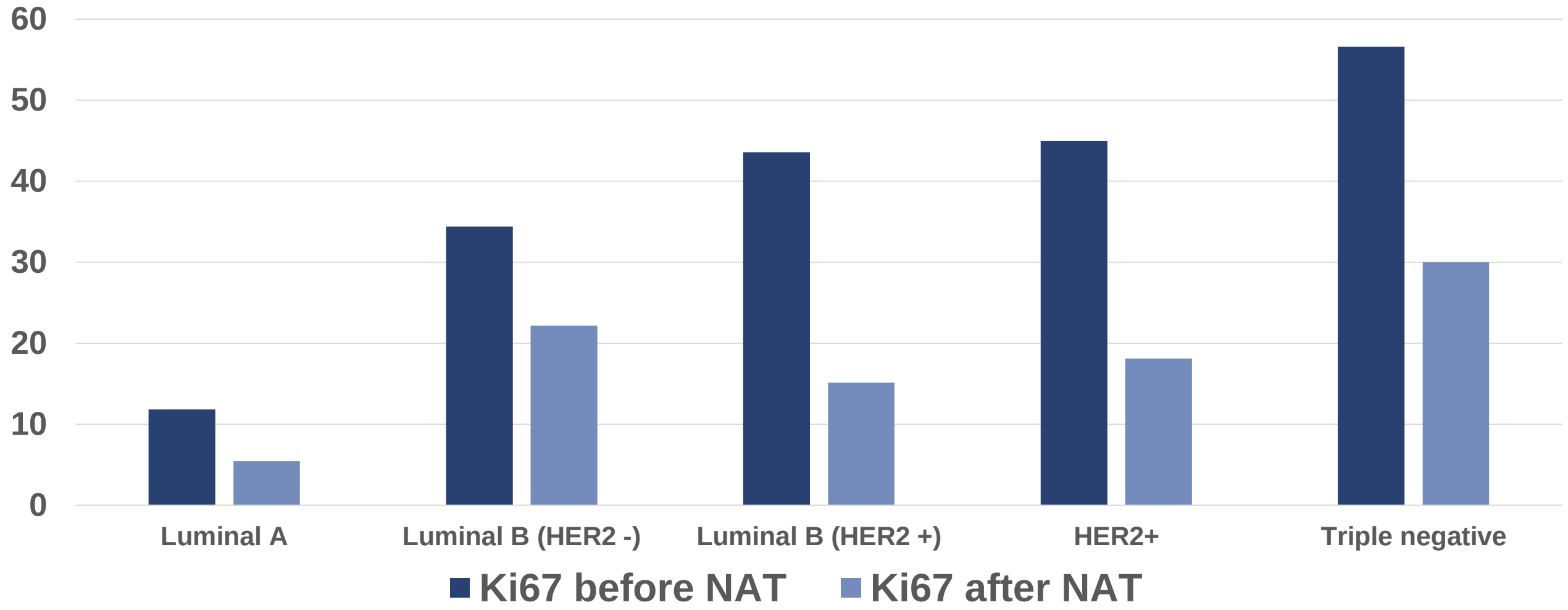


www.mdanderson.org/breast-cancer_RCB

Results of Ki67 evaluation

Subtype	No cases	Ki67 before NAT	pCR Ki67: 0%	Ki67 after NAT (w/o pCR cases)	Ki67 after NAT (with pCR cases)	Ki67 average reduction
Luminal A	14	11,85%	0 cases/0%	5,42% (1-10%)	5,42%	6,43%
Luminal B (HER2 -)	14	33,4%	1 case /7%	23,85% (6-44%)	22,15%	11,25%
Luminal B (HER2 +)	52	43,6%	16 cases /30,8%	21,88 (2-65%)	15,14%	28,2%
HER2 +	10	45%	4 cases/40%	30,2 (16-49%)	18,12%	26,88%
Triple Negative	58	56,6%	15 cases /25%	40,41 (1-100%)	30%	26,6%

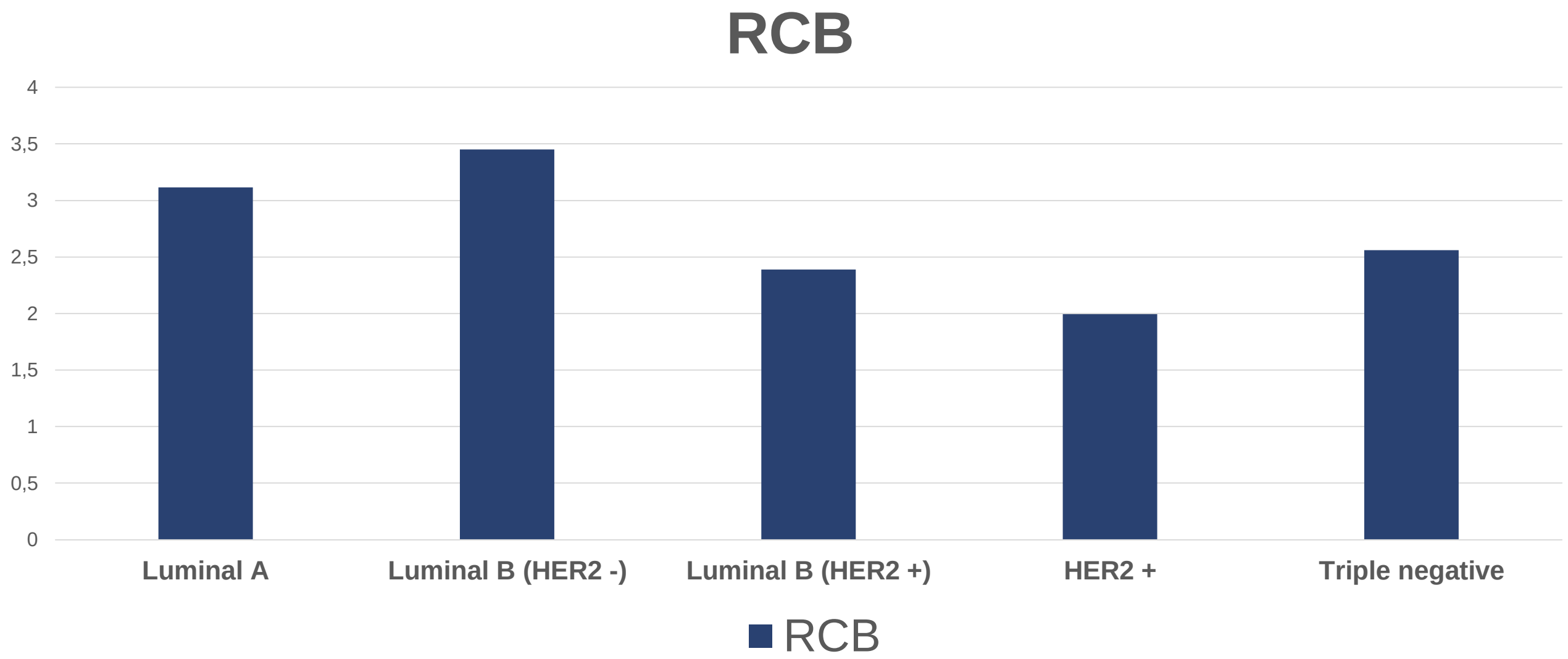
Ki67 reduction in subtypes after NAT



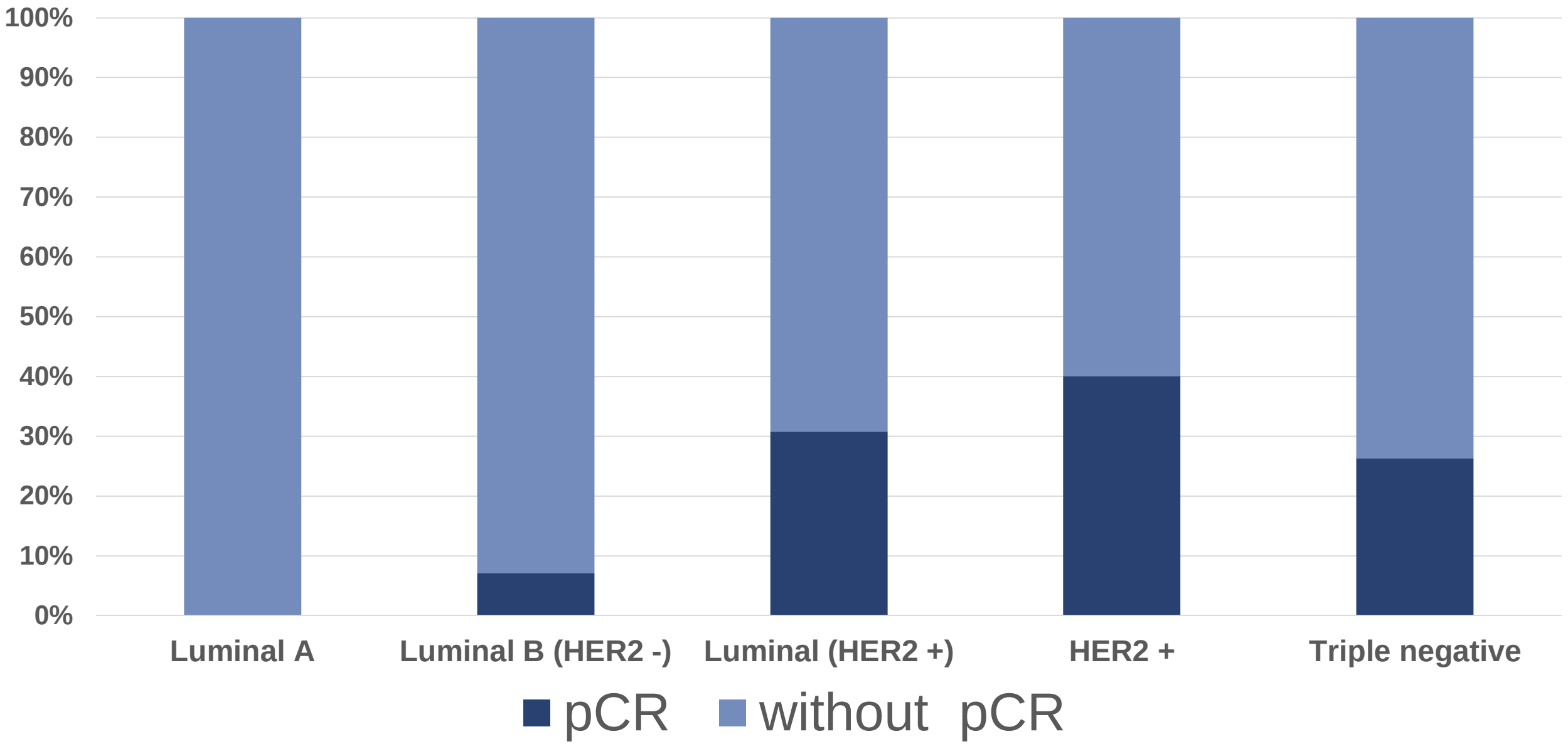
Cellularity and RCB values in subtypes

Subtype	No cases	Cellularity after NAT (RCB)	Residual Cancer Burden
Luminal A	14	72%	3,117
Luminal B (HER2 -)	14	68%	3,452
Luminal B (HER2 +)	52	36%	2,389
HER2 +	10	24%	1,993
Triple Negative	58	31%	2,559

Residual cancer burden in intrinsic subtypes



pCR in the intrinsic subtypes



Conclusion

- The Ki67 index predicts the response to neoadjuvant treatment assessed as the calculated Residual Cancer Burden value, percentage of pCR and the decrease in cellularity in HER2 positive subtypes (both) and triple-negative (ductal) subtype. Best prediction in our study is for Ki67 index higher then 35%
- New prognostic indexes required more precise measurements of Ki67 index in breast carcinoma. Evaluation Ki67 in 500 cell of invasive carcinoma gives sufficient reproducibility of results (and takes less than 5 minutes).
- Visual estimation is not enough for prognostic indexes.