Dr. Adnan Aydiner
Dr. Ahmet Kizir
Dr. Vahit Ozmen
Dr. Merdan Fayda

Summary of St Gallen consensus 2013
Istanbul University Institute of Oncology, 29 Mart 2013

Geographical and professional composition of the consensus panel at St Gallen 2013

A total of 48 breast cancer experts (including 2 chairmen) from 21 countries worldwide	
Europe	25
USA, Canada and South America (Peru)	17
Austal-Asia (Australia, China and Japan)	6

Professional composition	
Medical oncology	27
Surgery, gynaecology	13
Pathology, basic research	4
Radio-oncology	2
Statistics, epidemiology	2

Conference Topics

- Surgery
- Radiation therapy
- Pathology
- Adjuvant systemic therapy
- Follow up

Conference Topic

Surgery

When considering breast conserving surgery which factors are contraindication?

Selection Criteria for BCT

Biological

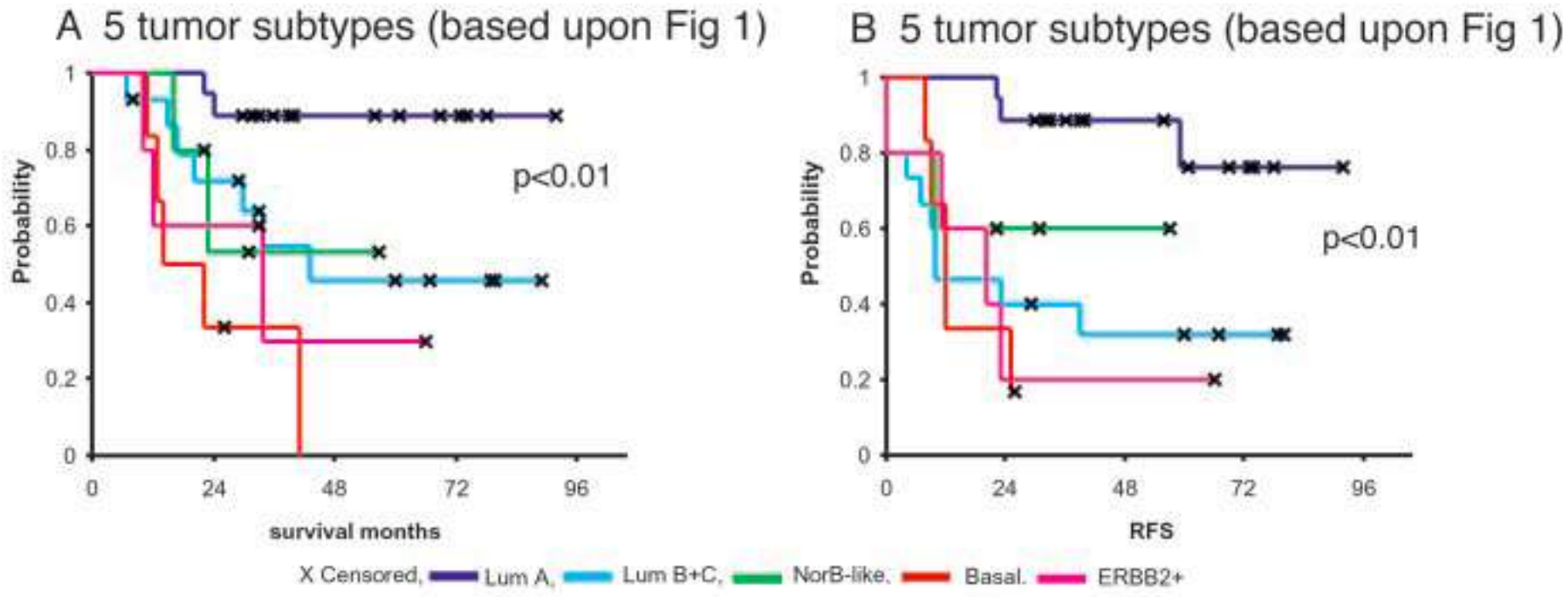
- Histology
- Grade
- Nodal status
- ER
- HER2

Mechanical

- **Extent of disease in breast**
  - Negative margins
  - Diffuse calcifications
  - Multicentricity
- **Ability to give RT**
  - Prior RT
  - Active SLE, scleroderma

Morrow M, 13th St. Gallen IBCC, 2013

DFS and OS by Subtype



Morrow M, 13th St. Gallen IBCC, 2013

Sørlie T, et al. Proc Natl Acad Sci USA. 2001;98(18):10869-10874

Characteristics By Subtype

n=6072

	ER/PR+ HER2-	ER/PR+ HER2+	ER- HER2+	ER/PR- HER2-	P-value
%High Grade	29	62	88	85	<.0001
%Multifocal/centric	27	30	37	22	<.0001
%EIC	15	25	27	9	<.0001

Morrow M, 13th St. Gallen IBCC, 2013

Molecular Subtype and LR After BCT

Study	Time	n	%LR			
			Lum A	Lum B	HER2*	Basal
Millar	5 yr	498	1.0	4.3	7.7	9.6
Voduc	10	1461	8	10	21	14
Arvold	5yr	1434	0.8	2.3	10.9	8.8

* No adjuvant transtuzumab

Morrow M, 13th St. Gallen IBCC, 2013

Molecular Subtype and LR After Mastectomy

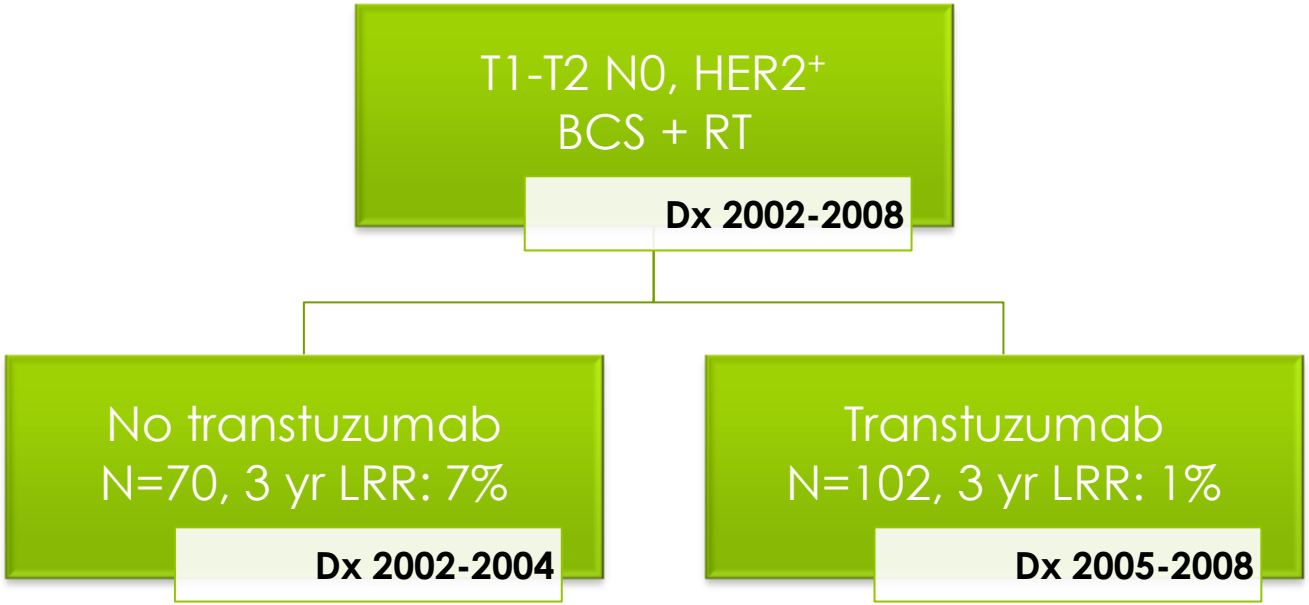
Study	Time	n	%LR			
			Lum A	Lum B	HER2*	Basal
Kyndi	5 yr	498	2	3	13	21
Voduc	10	2985	8	14	17	19

* No adjuvant transtuzumab

Morrow M, 13th St. Gallen IBCC, 2013

Effect of Transtuzumab on LRR in HER2+ Patients

Memorial Sloan-Kettering Cancer Cencer



p=0.01

Morrow M, 13th St. Gallen IBCC, 2013

Kiess AP et al. Cancer 118:1982-1988, 2012

Is there evidence in the higher-risk triple negative subset that bigger surgery is better surgery?

LRR in triple negative Breast Cancer T1, T2 N0

	BCT (n=223)	MRM, No RT (n=235)	p
5 yr LRR free survival	96%	90%	0.022

- **Multivariate HR: MRM vs BCT**
  - 2.52, 95% CI 1.11-5.72; p=.027
  - 2.53, 95% CI 1.12-5.75; p=.026

Morrow M, 13th St. Gallen IBCC, 2013

The proven risk factors for LR after BCT (HR>2)

- Gross incomplete resection (invasive and DCIS): everybody knows
- No radiotherapy
- Young age (<35 yrs)
- Biology: BRCA1/2, gene signature?

Rutgerz E, 13th St. Gallen IBCC, 2013

Conclusions

- Locoregional outcomes vary by molecular subtype.
- Bigger surgery does not overcome bad biology.
- Effective systemic therapy decreases LR.
- Increasingly effective multimodality therapy offers
- The chance to decrease surgical morbidity.

Morrow M, 13th St. Gallen IBCC, 2013

Who should not have BCT?
To conclude for coming Monday:

Family history of BC:

- No

BRCA1/2 mutation carrier:

- Not in itself, risk must be discussed

Involved margins:

- YES, after maximal/optimal atempt to achieve clear margins

Rutgerz E, 13th St. Gallen IBCC, 2013

Who should not have BCT?
To conclude for coming Monday:

No posibility for adequate radiotherapy:

- YES

Unfavorable biology on gene expiresion profiling:

- ?, needs futher research

Patient prefers mastectomy:

- YES, provided patient is informed well in a neutral way

Rutgerz E, 13th St. Gallen IBCC, 2013

When considering breast conserving surgery which of the following factors are basic contraindication?

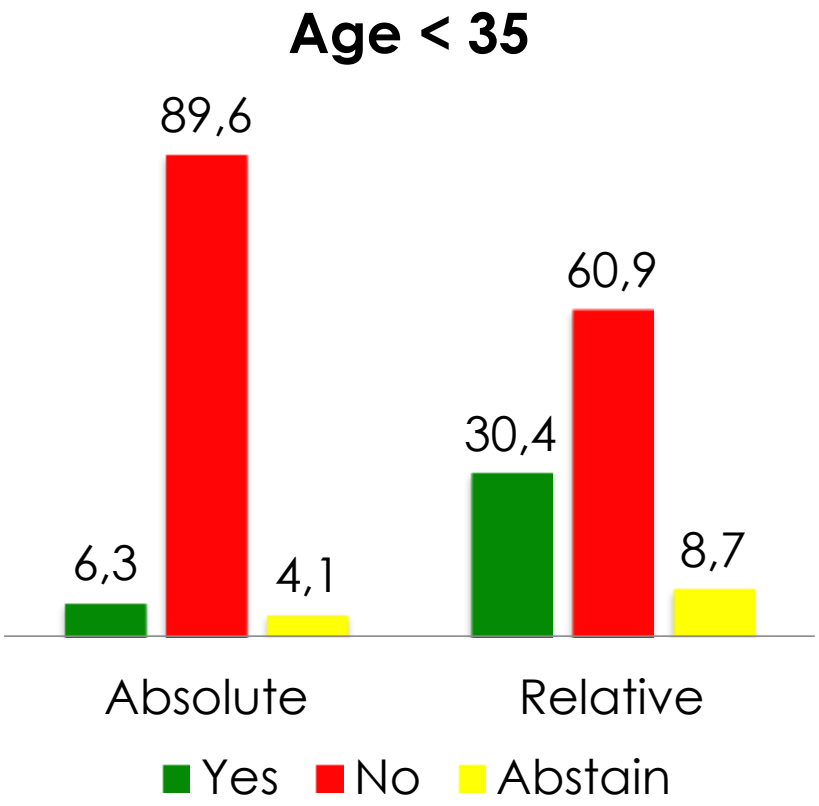
1	Young Age <35; <40
2	Extensive or diffuse microcalcifications
3	Multifocal disease
4	Multicentric disease
5	Tumor close to nipple
7	Extensive vascularization
8	Extensive intraductal component
9	Lobular histology

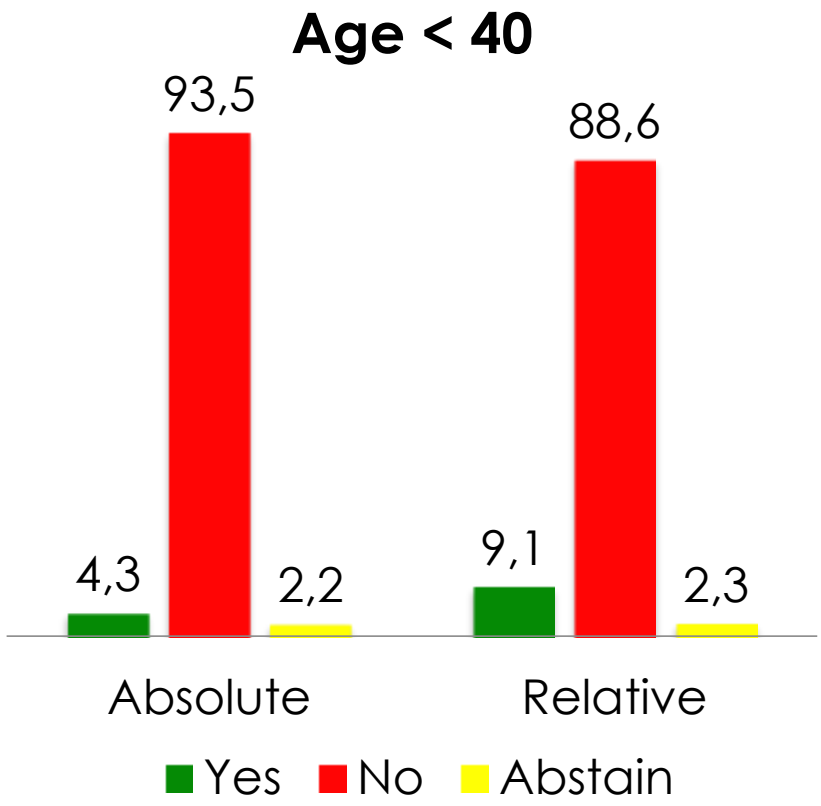
When considering breast conserving surgery the following factor is contraindication

Important: In the following questions, answering Yes in "Absolute" meant that the panelist had to abstain in the subsequent question on "Relative".

For abstain: Panelists were advised to abstain if they felt that the issue had insufficient data, or if the panelist did not consider themselves an expert in that particular issue, or if there was a potential conflict of interest.

When considering breast conserving surgery the following factor is contraindication





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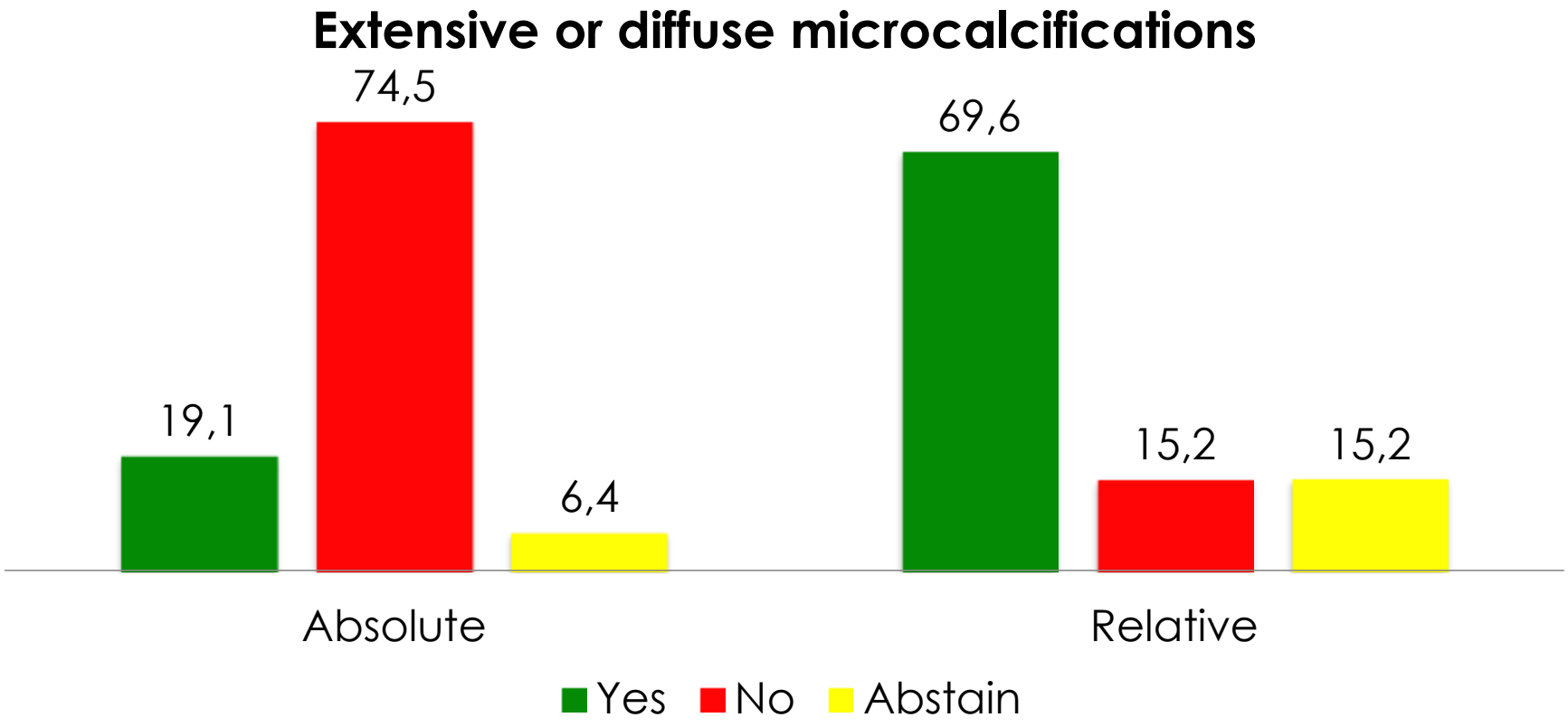

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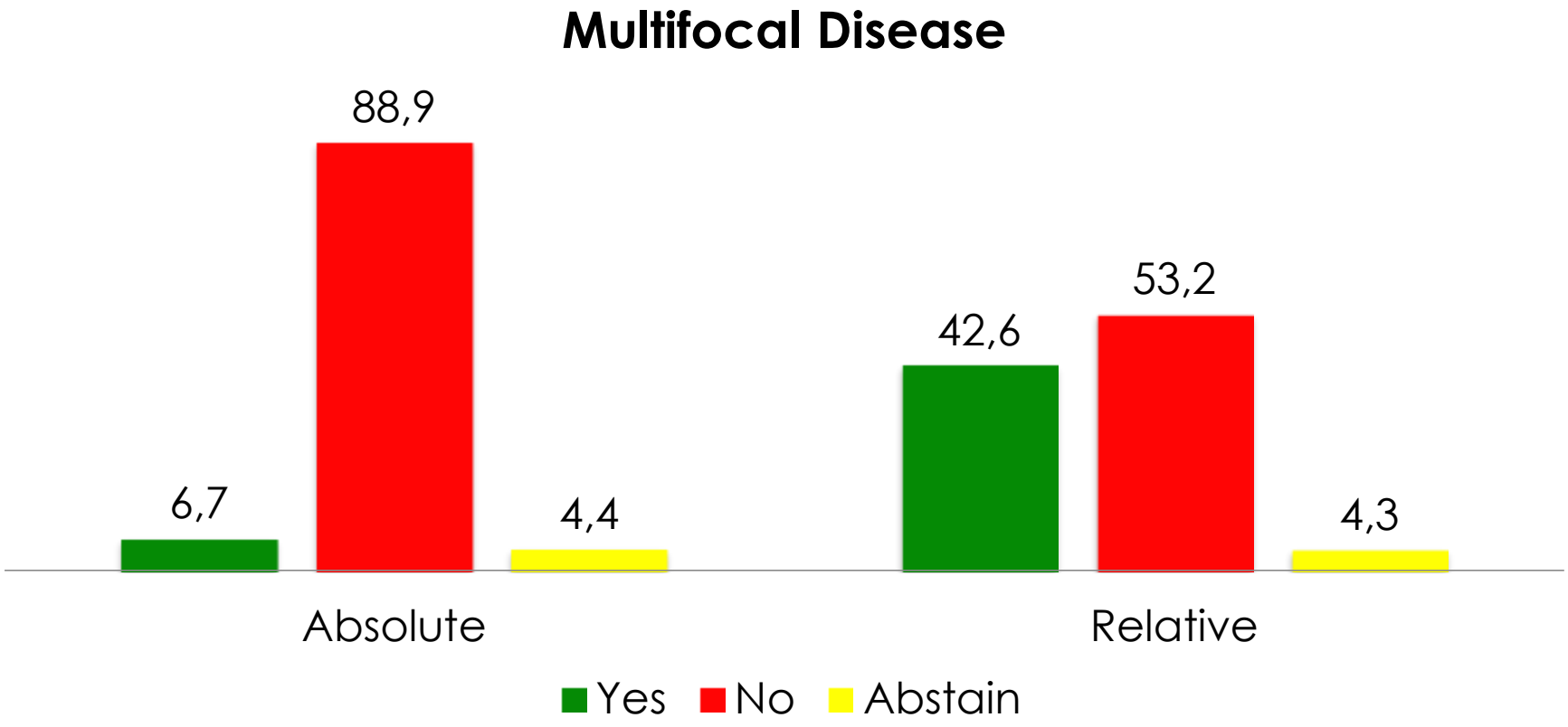

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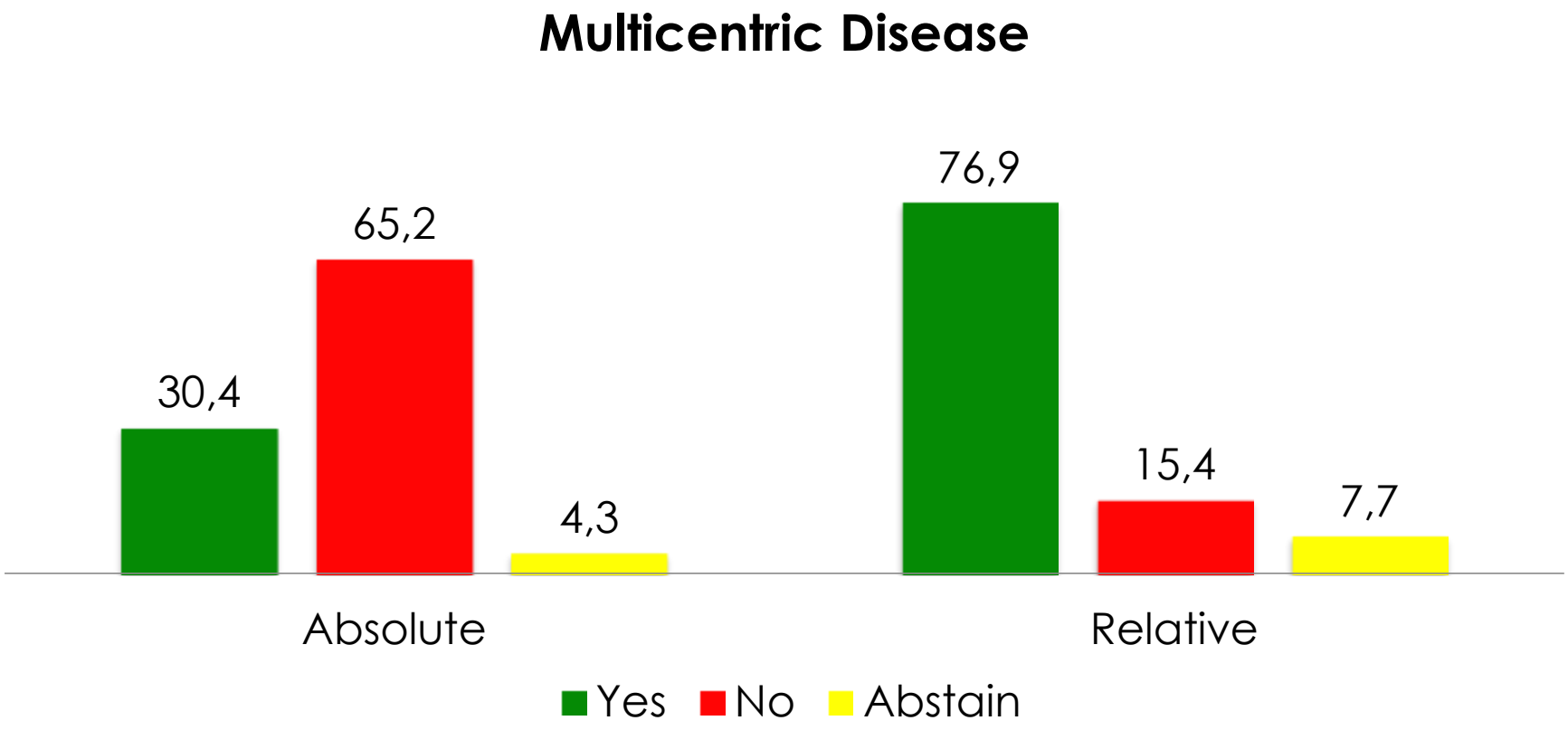

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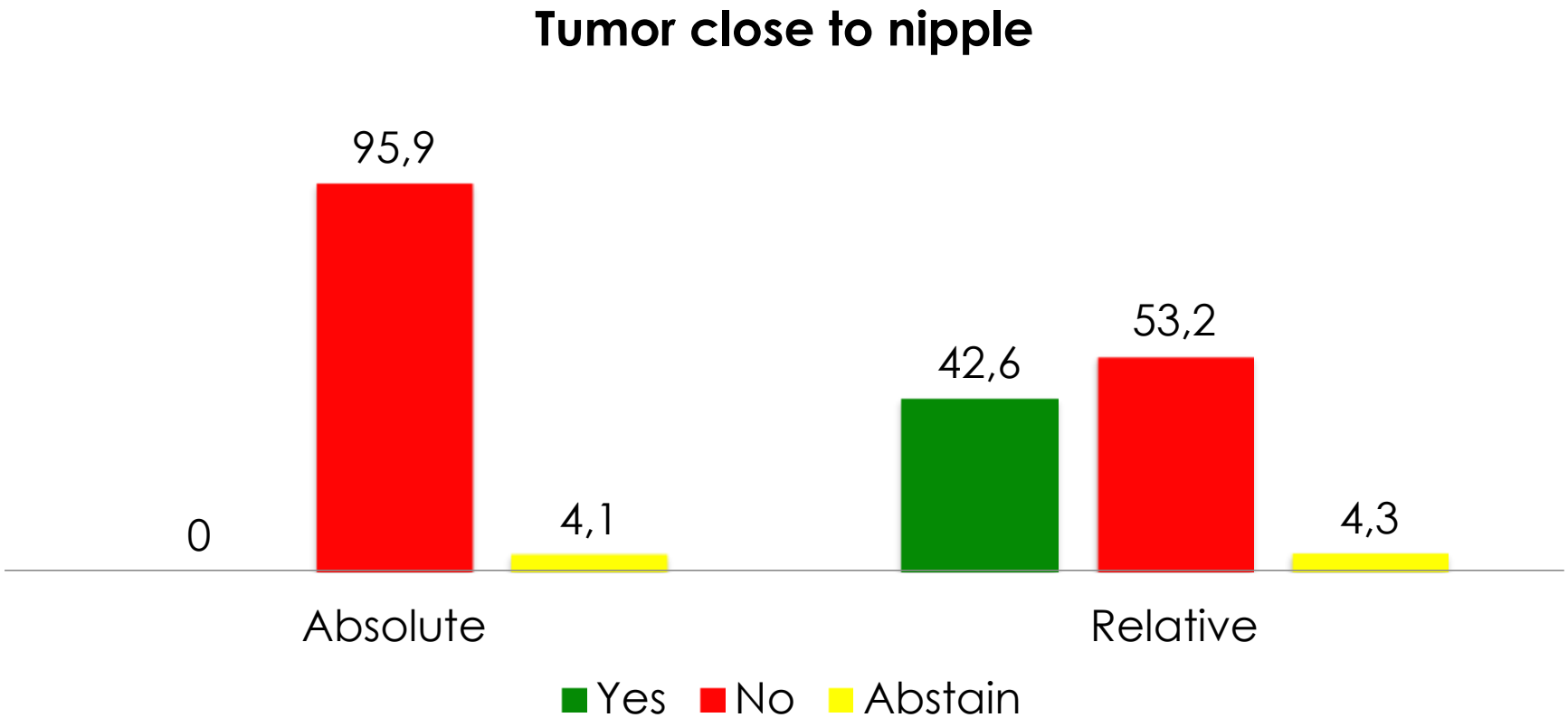

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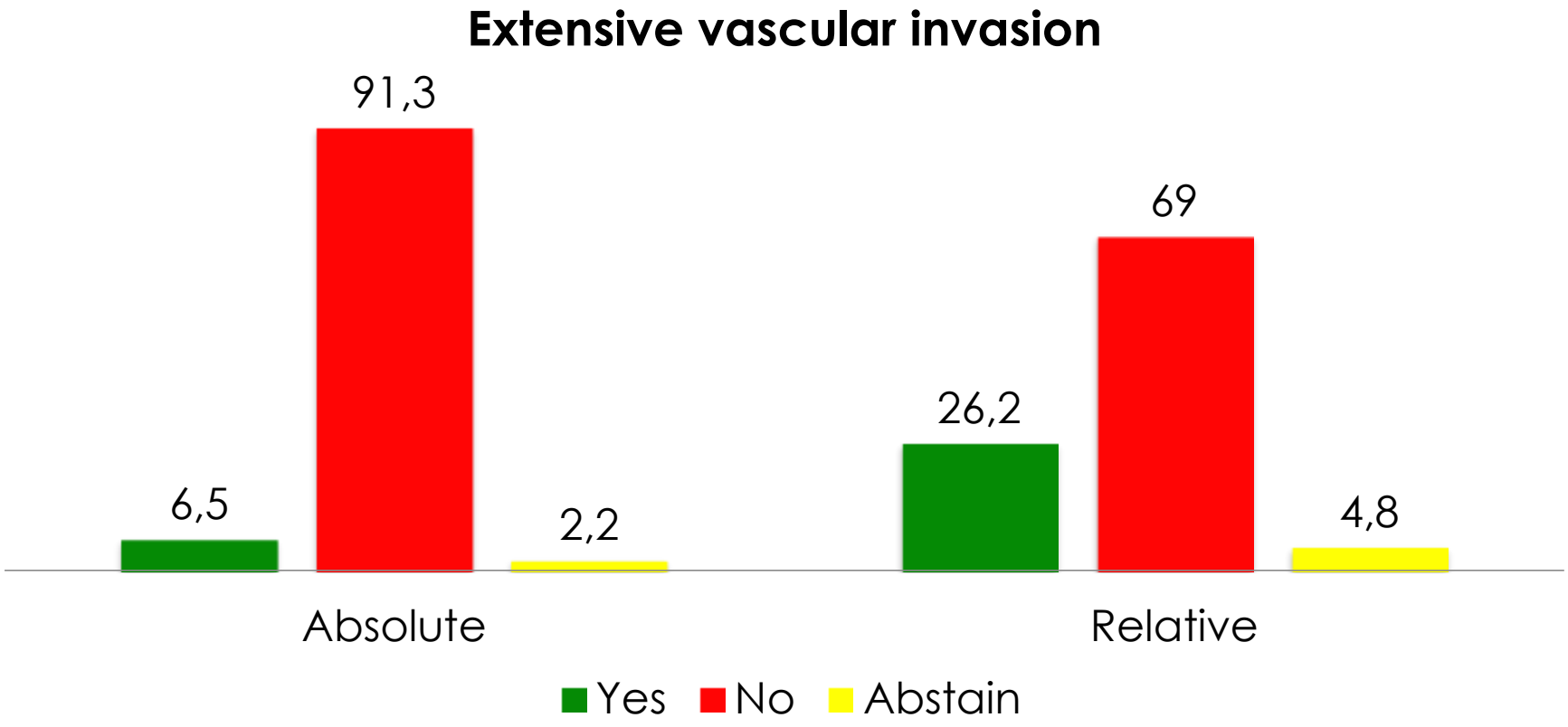

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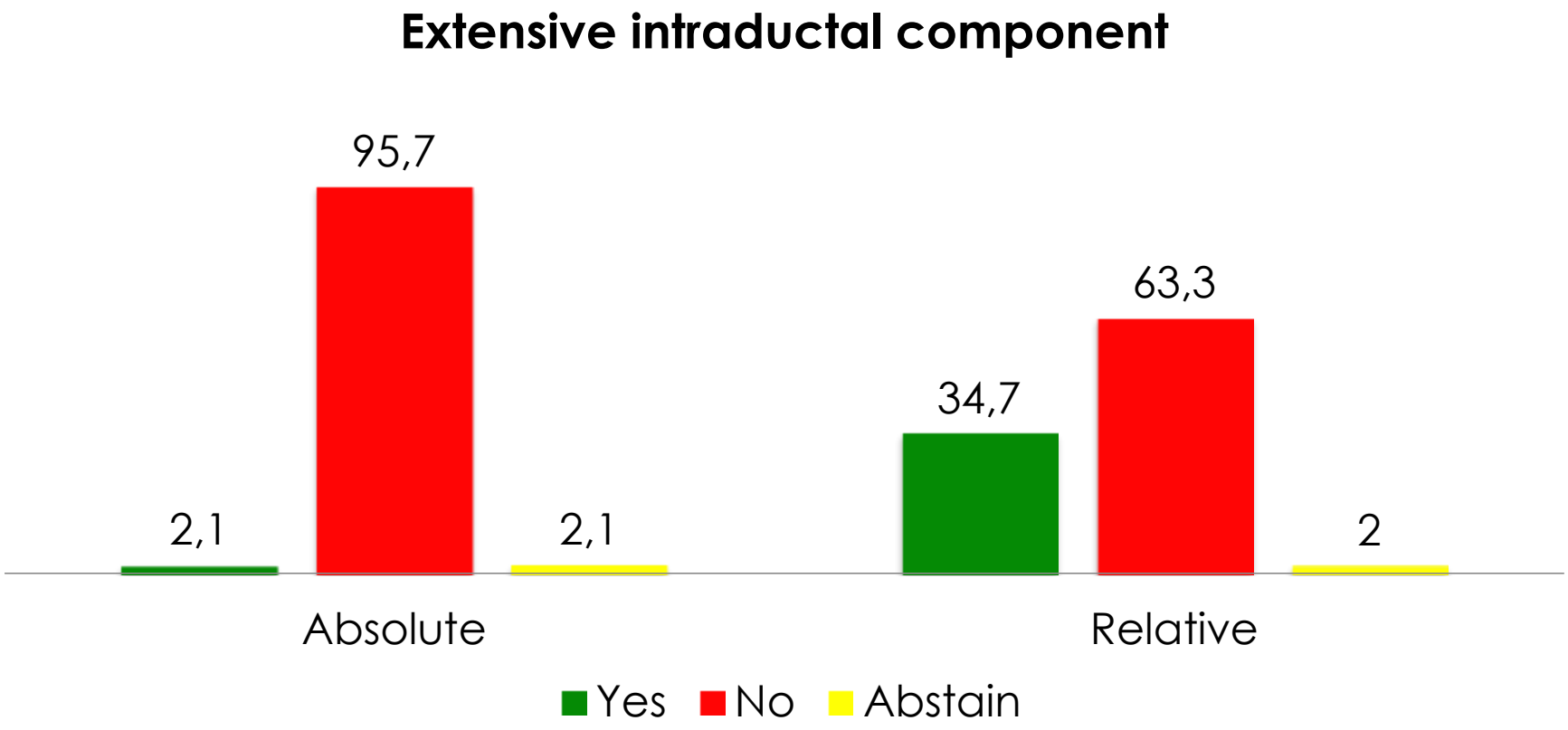

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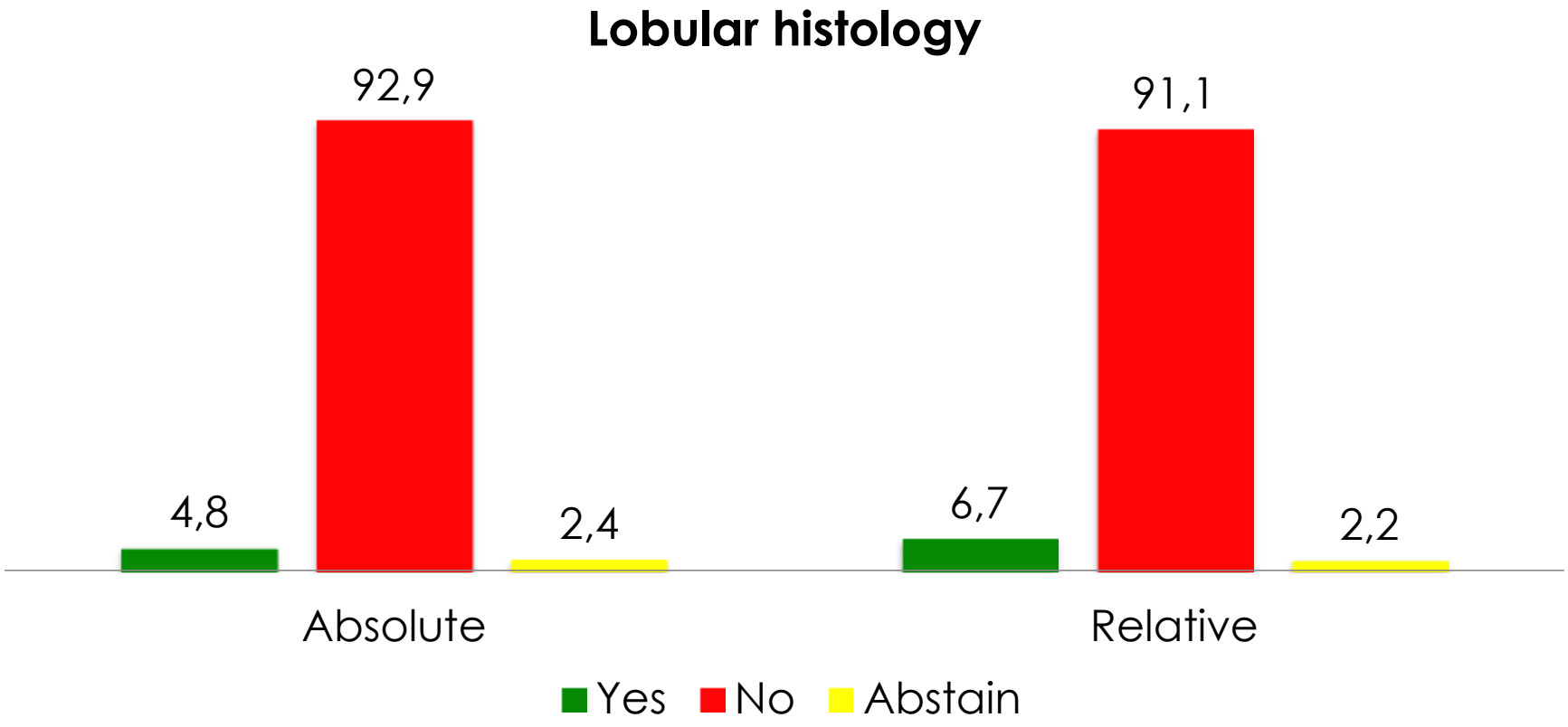


consensus

When considering breast conserving surgery the following basic factors ARE NOT ABSOLUTE contraindications.

1	Young Age <35; <40
2	Extensive or diffuse microcalcifications
3	Multifocal disease
4	Multicentric disease
5	Tumor close to nipple
7	Extensive vascularization
8	Extensive intraductal component
9	Lobular histology

consensus

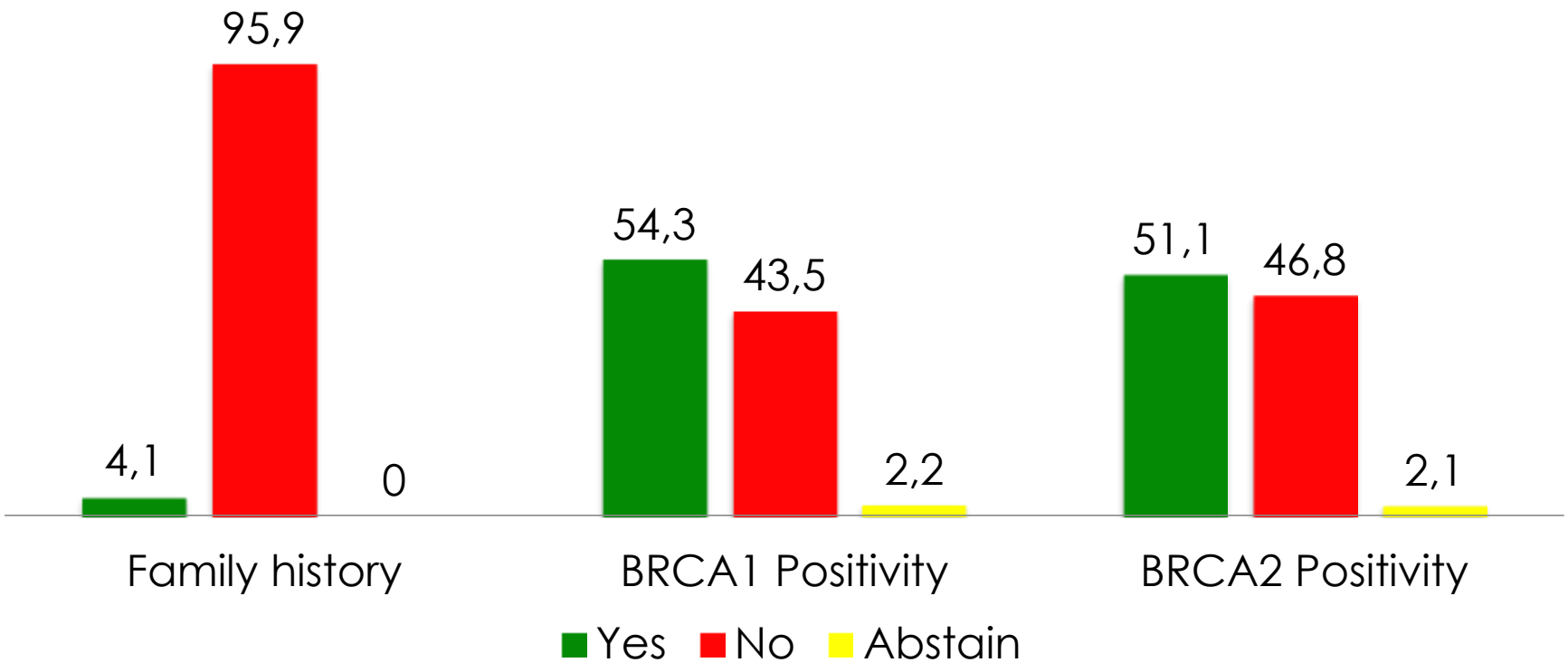
When considering breast conserving surgery the following basic factors are RELATIVE contraindications.

1	
2	Extensive or diffuse microcalcifications
3	
4	Multicentric disease
5	
7	
8	
9	

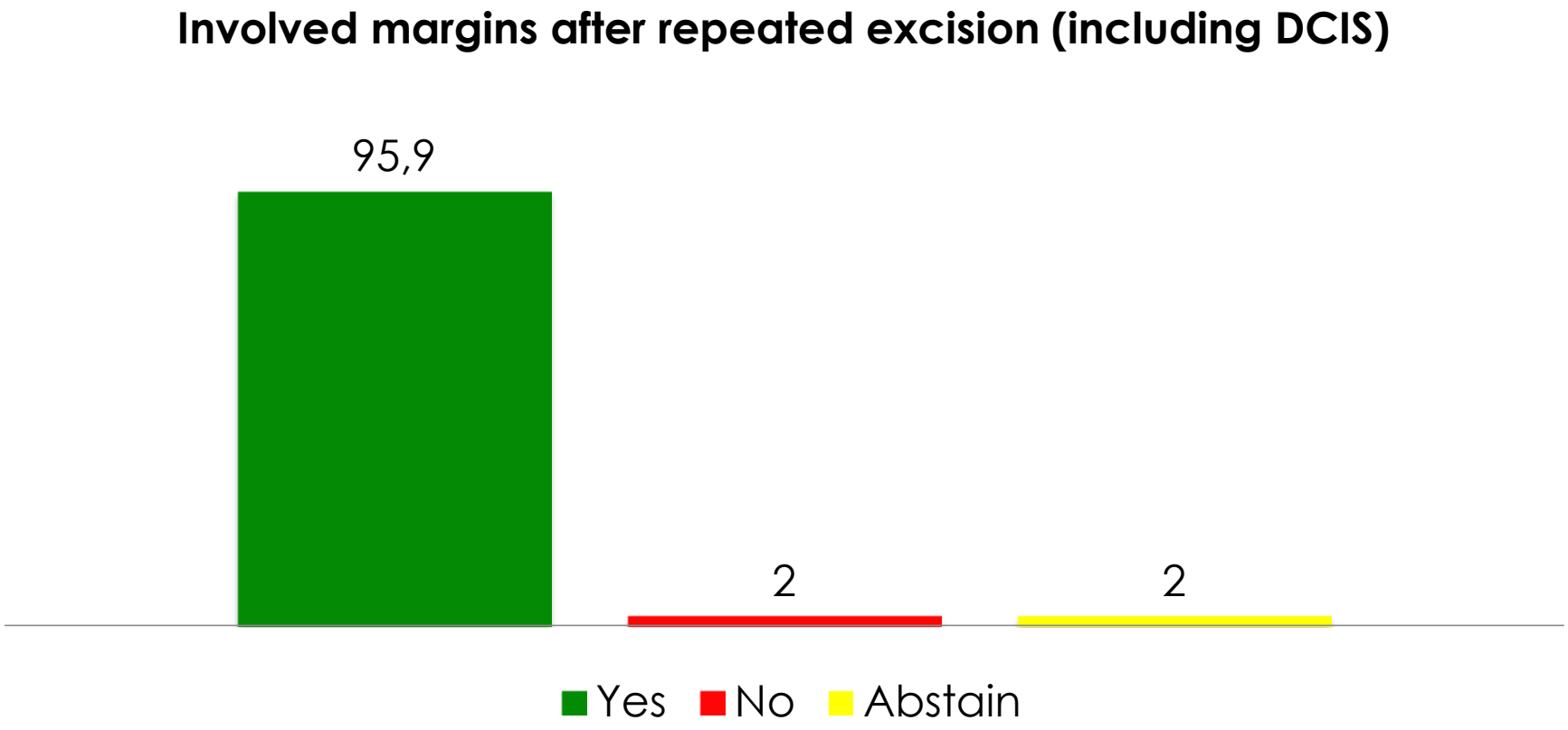
When considering breast conserving surgery which of the following factors are relative contraindications?

1	Family history
2	BRCA1 positivity
3	BRCA2 positivity
4	Involved margins after repeated excisions (including DCIS)
5	Unfavourable biology on gene expressing/sequencing
6	contraindications to breast irradiation that should follow breast conserving therapy

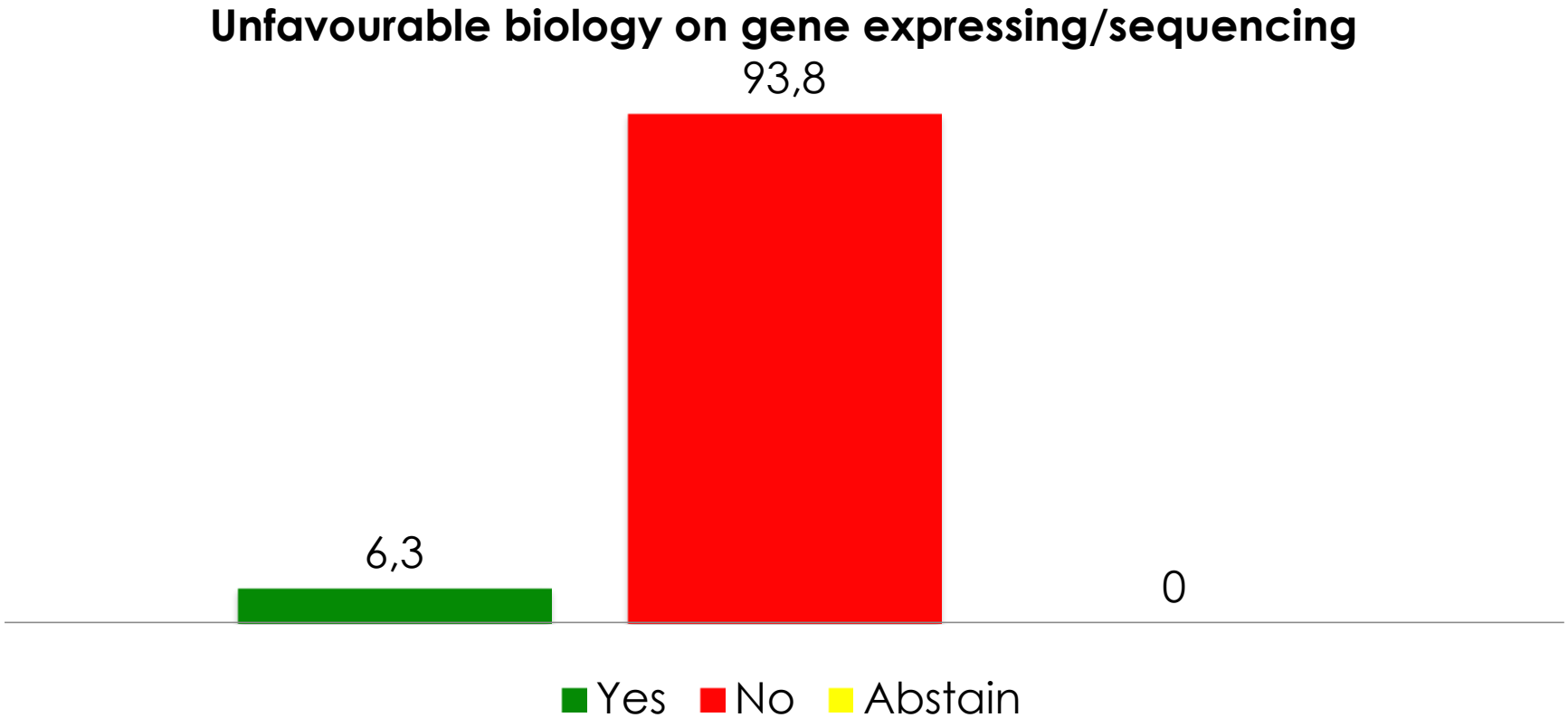
When considering breast conserving surgery the following factor is relative contraindication.



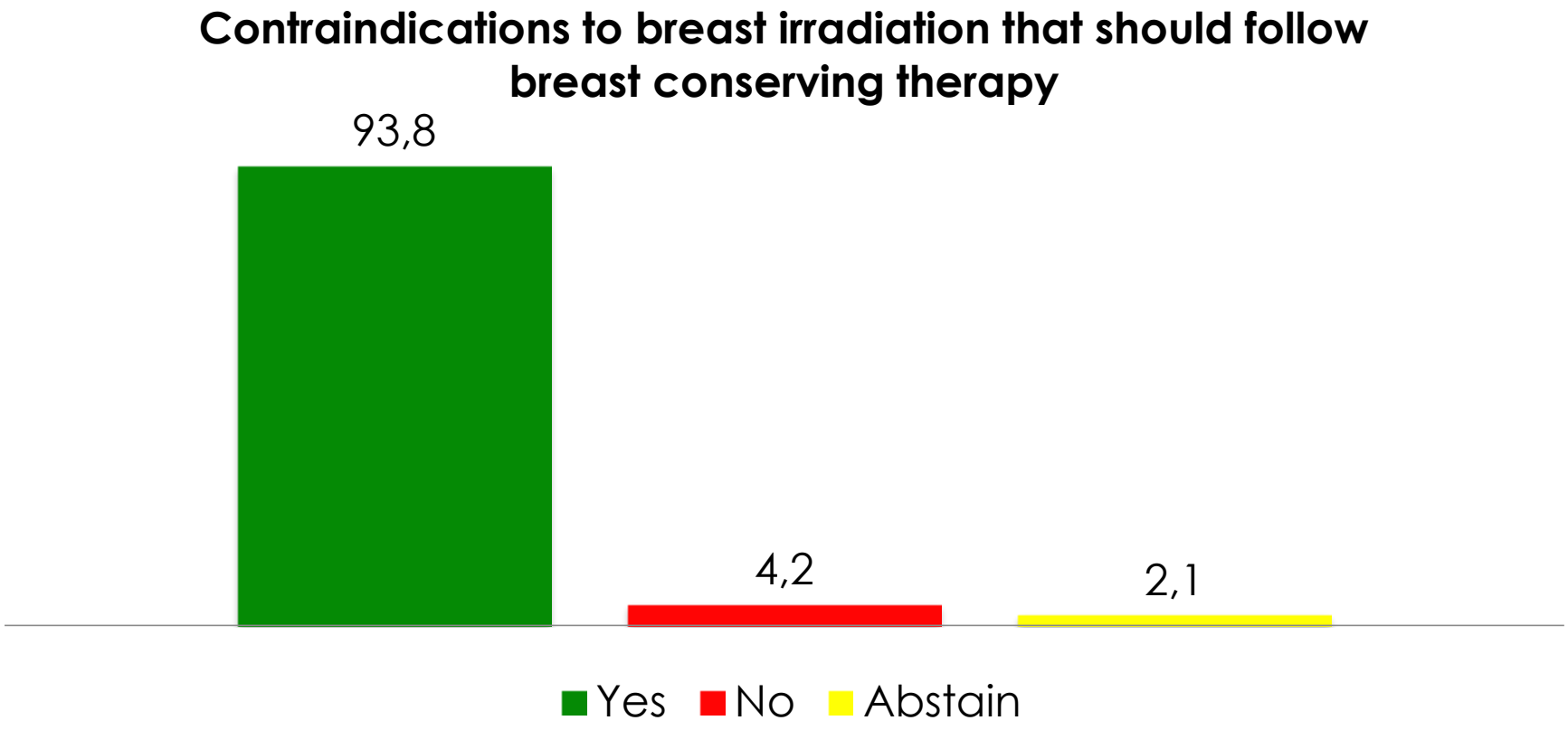
When considering breast conserving surgery the following factor is relative contraindication.



When considering breast conserving surgery the following factor is relative contraindication.



When considering breast conserving surgery the following factor is relative contraindication.



consensus

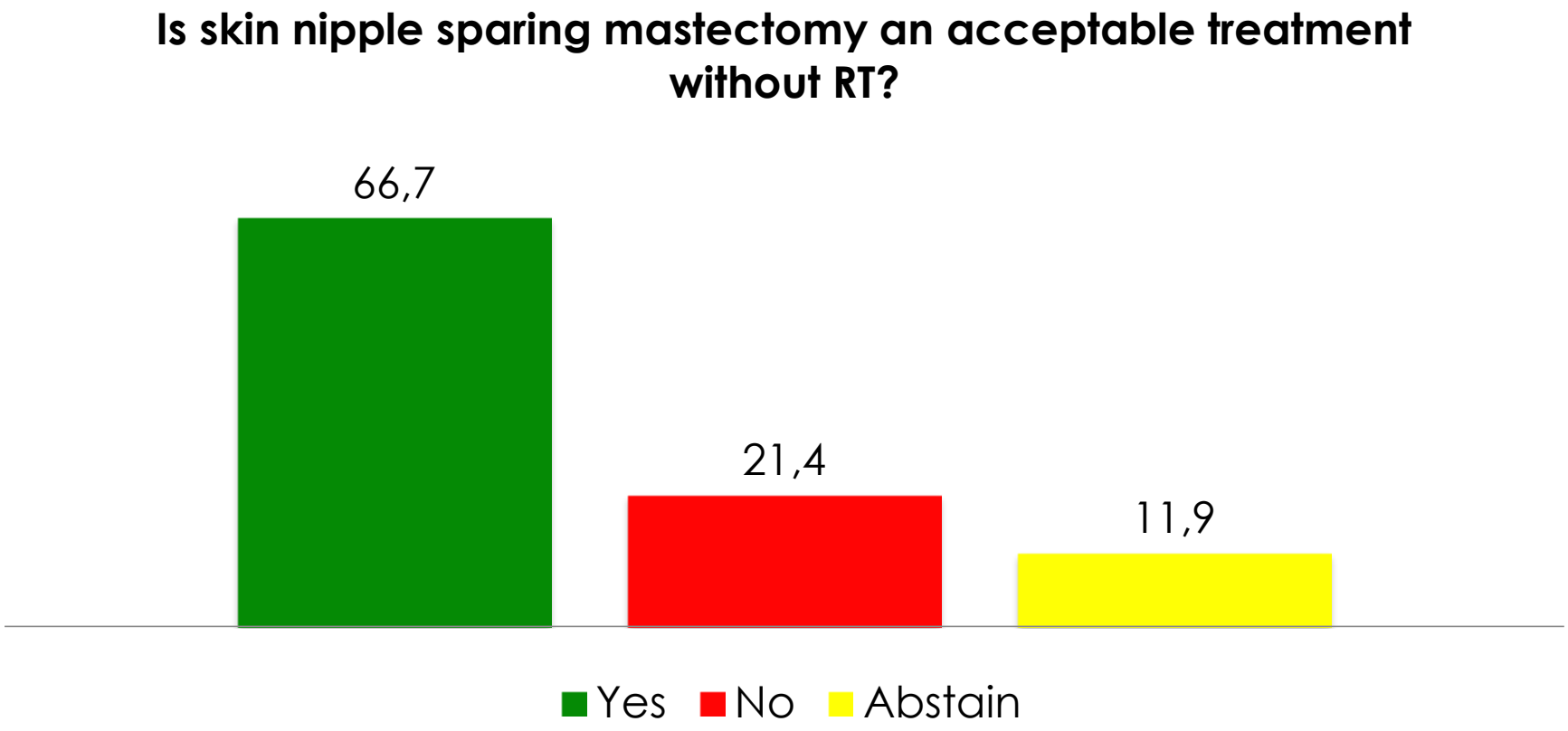
When considering breast conserving surgery the following factors are relative contraindications.

1	
2	BRCA1 positivity
3	BRCA2 positivity
4	Involved margins after repeated excisions (including DCIS)
5	
6	contraindications to breast irradiation that should follow breast conserving therapy

Comments

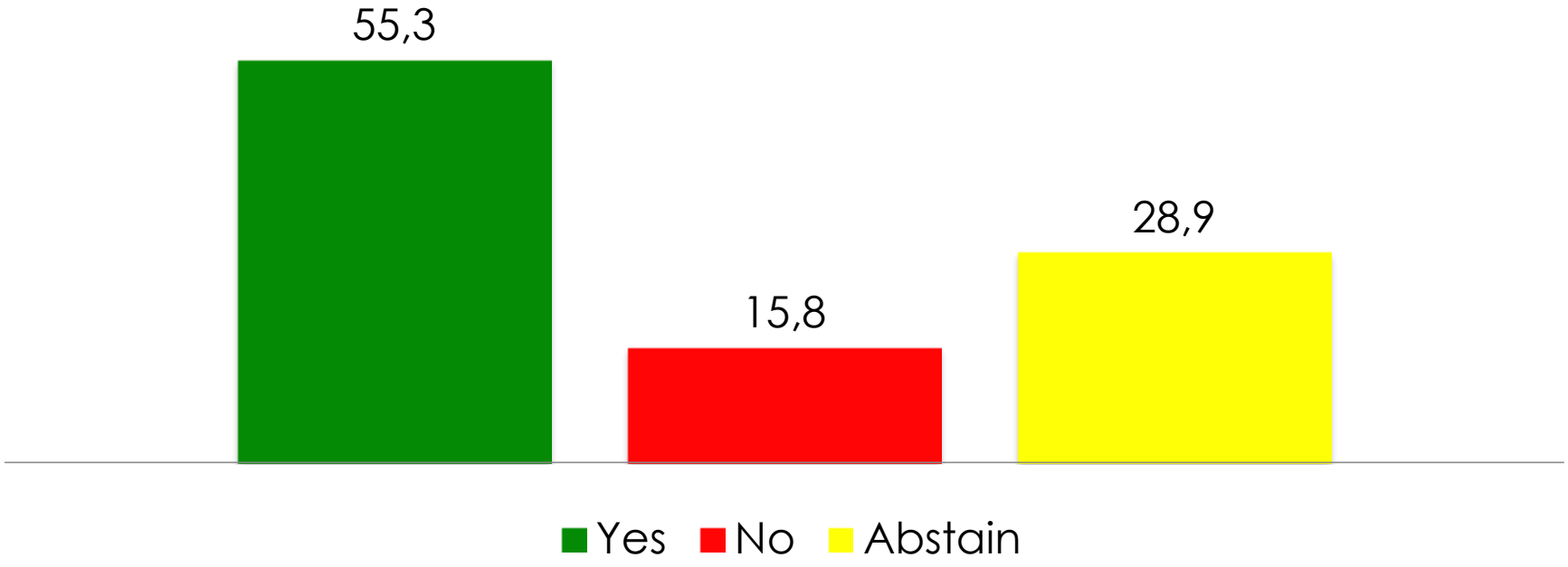
Michael Gnant said that he was very happy about this vote because the panel did not identify a single absolute contraindication for breast conservation. He was also happy that, for the first time, we have moved away from a formulistic definition of who needs to have mastectomy.

Surgery of the primary breast cancer

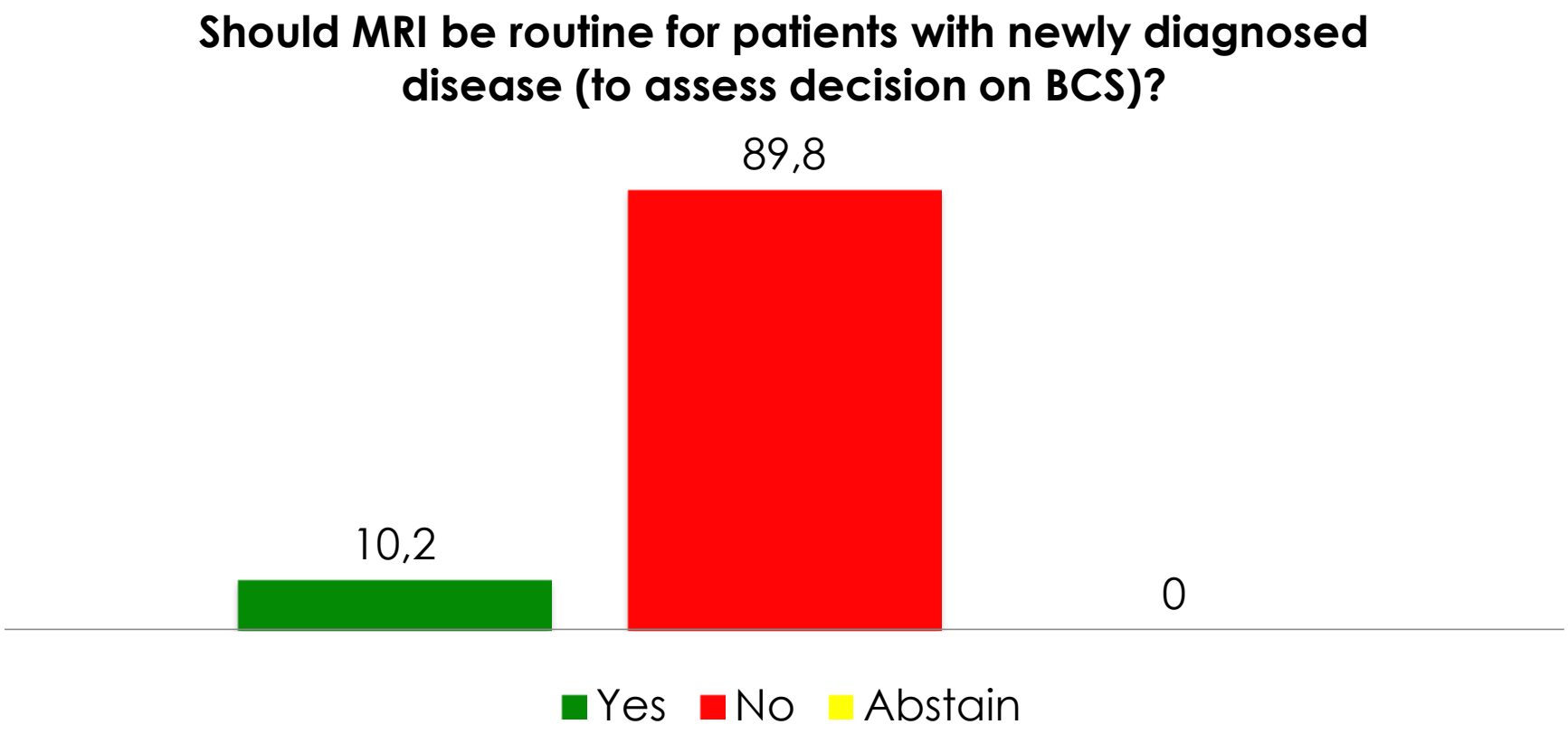


Surgery of the primary breast cancer

Is skin nipple sparing mastectomy an acceptable treatment if only margin toward nipple is tumor free and immediate reconstruction planned?

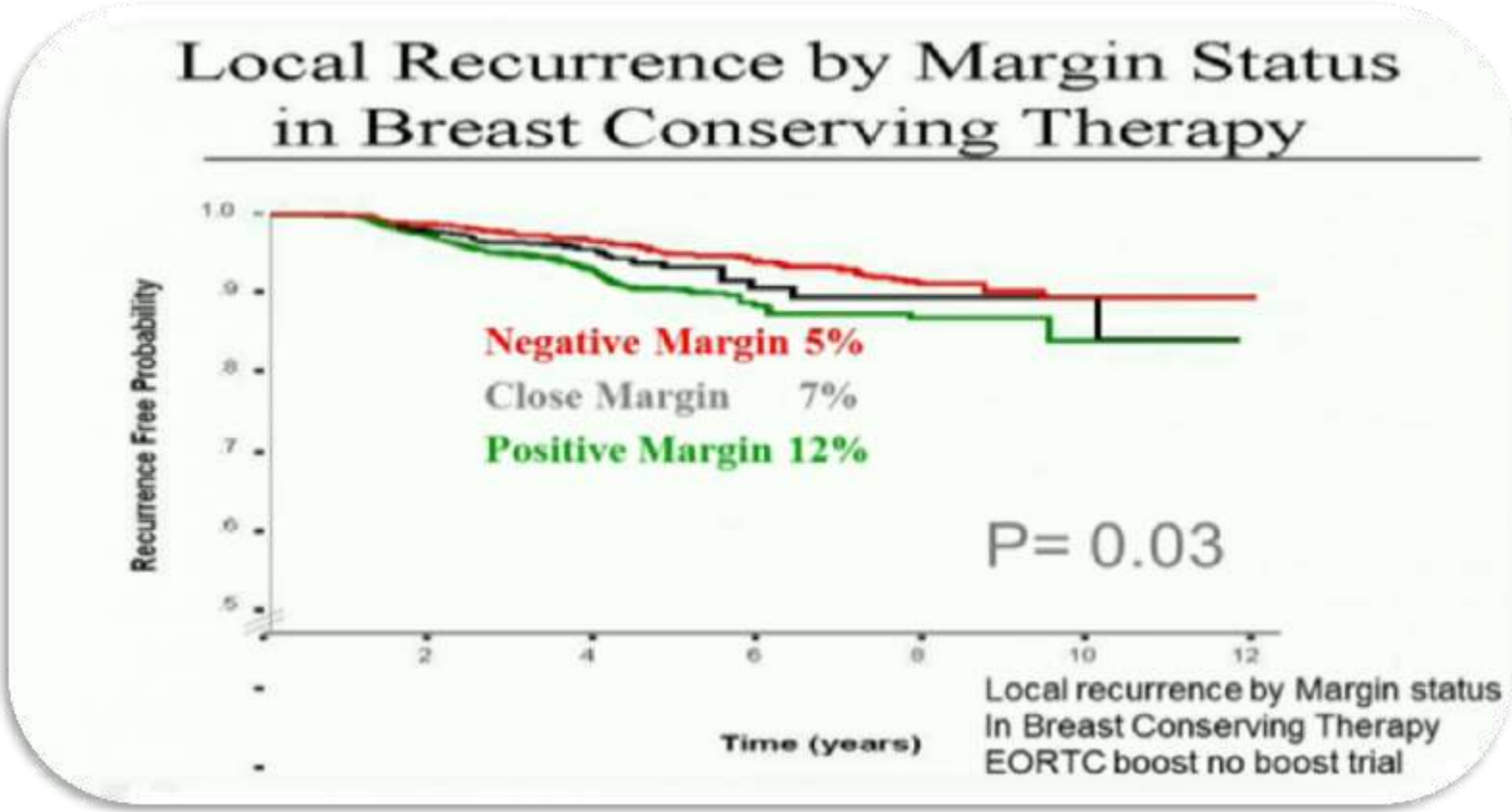


Surgery of the primary breast cancer



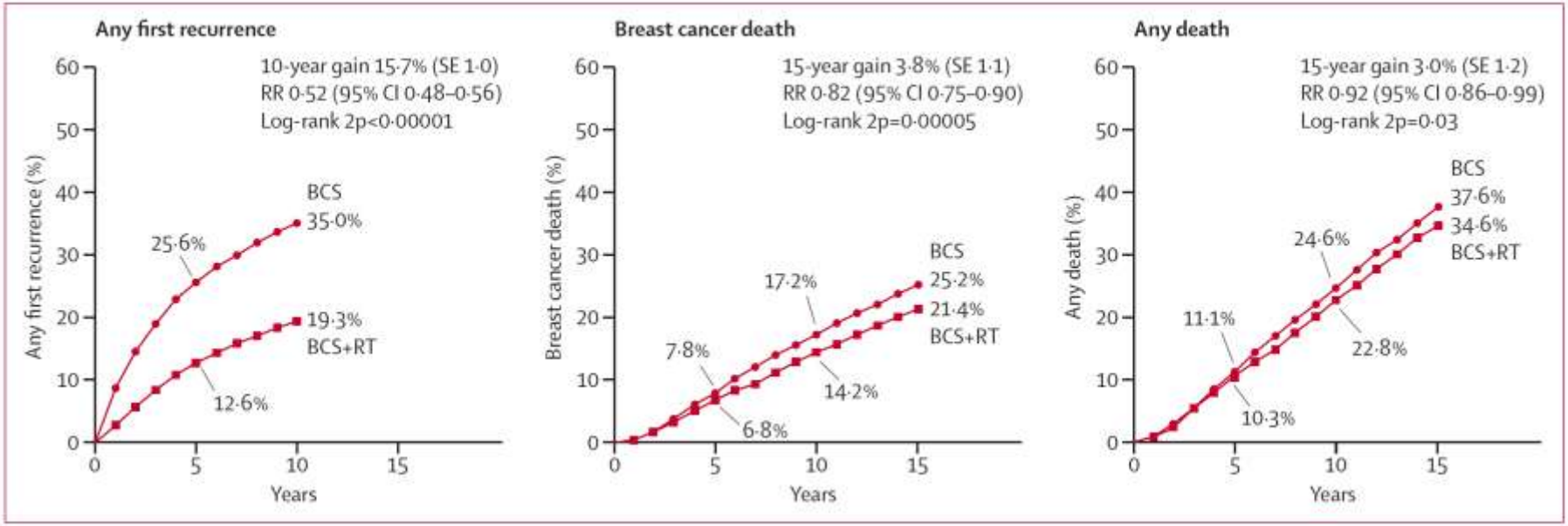
In woman undergoing breast conserving surgery what is the minimum appropriate surgical margin?

The proven risk factors for LR



Rutgerz E, 13th St. Gallen IBCC, 2013

Risk factors: no RT

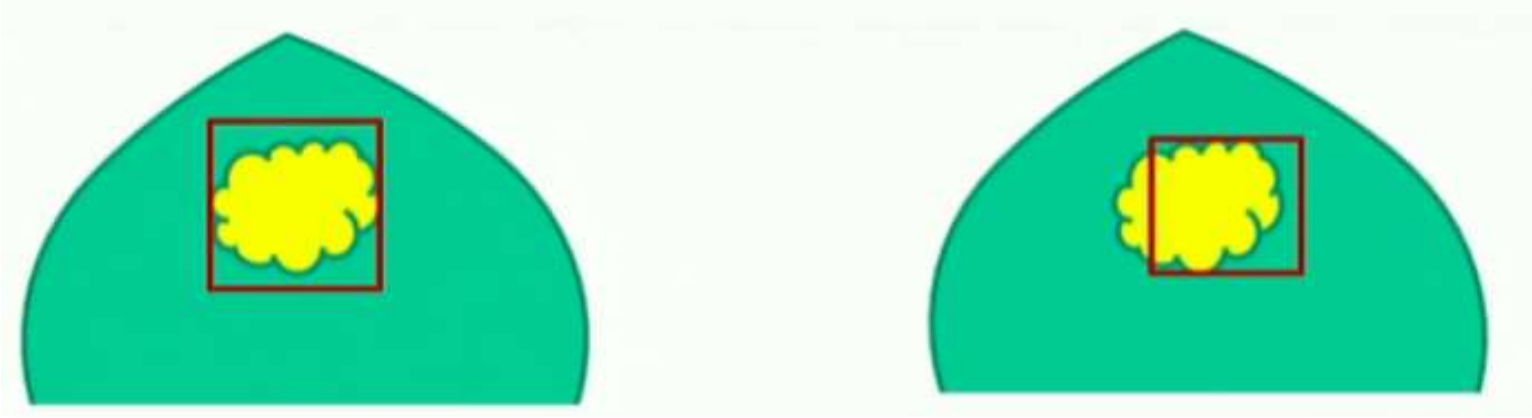


Effect of radiotherapy (RT) after breast-conserving surgery (BCS) on 10-year recurrence and 15-year breast cancer death: 10 801 women in 17 trials

Rutgerz E, 13th St. Gallen IBCC, 2013

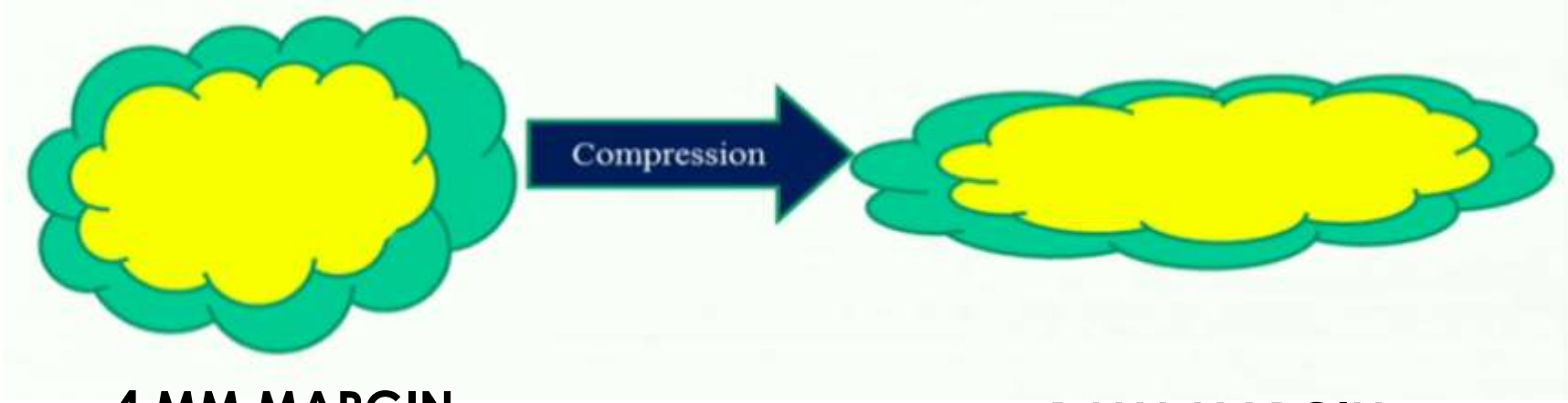
EBCTCG, Lancet 2011; 378: 1707–16

TWO POSITIVE MARGIN EXCISIONS



SPECIMEN IN OR

SPECIMEN IN PATHOLOGY



4 MM MARGIN

<1 MM MARGIN

What is a negative margin?

- No ink on tumor?
- 1 mm?
- > 1mm?
- >2mm?
- >5mm?

Close margin

"Close Margins" v.s. Wider Margins

Park	Joint Center	2000	No difference
Singletary	34 studies	2002	No difference
Houssami	21 studies	2010	No difference

Excision Goal: Avoid Positive Margins

- Relate margin width to size of tumor
- Neo-adjuvant chemo- or hormonal therapy >
- Careful margin evaluation in OR
- Thouch prep or frozen section before closing
- Shave biopsy of cavity margins
- Intra-operative ultrasound guidance
- Electromagnetic margin probes

In-op Ultrasound Guidance

	Positive margin rate
Palpation guided surgery	16.4 %
U/S guided surgery	3.3 %

Krekel NM, et al. Lancet oncol 2013; 14: 48-54.

Electro-magnetic Margin Probe
INVESTIGATIONAL

Dune Medical Devices, Inc

Particular Risk Groups
(not including BRCA Mutation Patients)

- Younger patients: <50, <40, <35 yrs
- "Triple negative" biology, basal profile
- Extensive DCIS in specimen
- Multifocal or multicentric primary
- Larger tumors
- Spotty response to neoadjuvant therapy

Conclusions

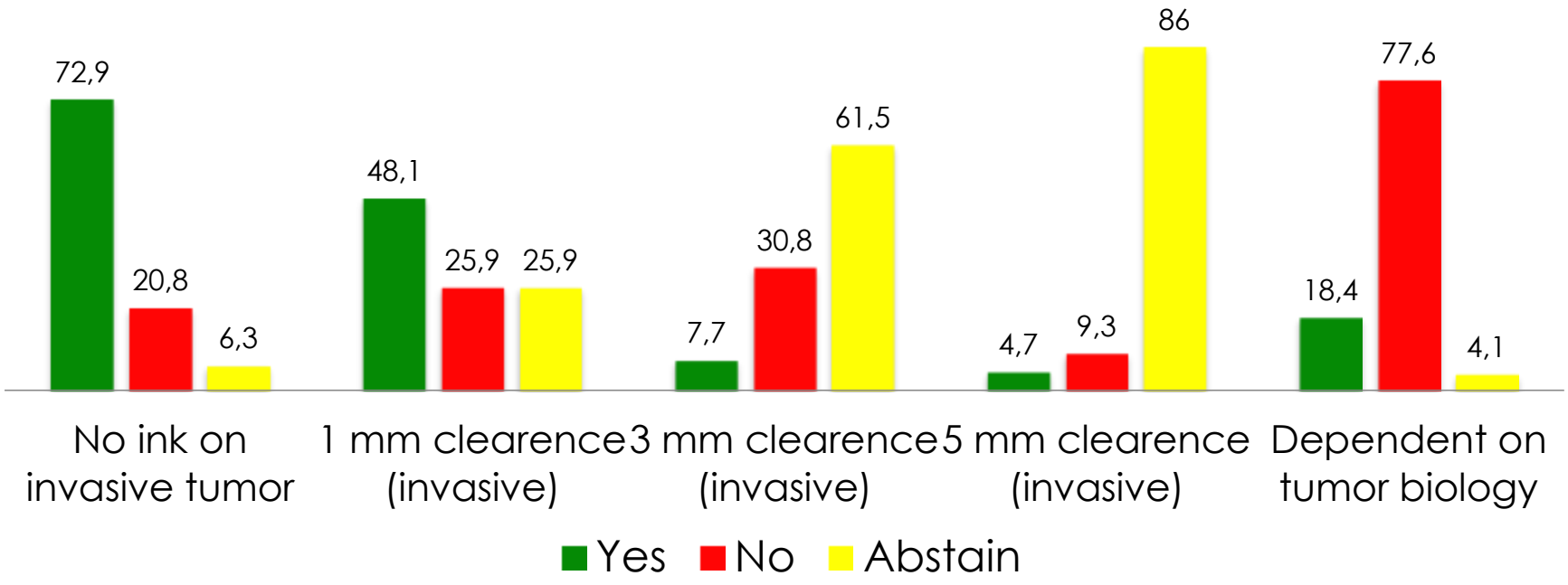
- Diagnose by core biopsy before attempting excision
- Integrate: tumor size and biology, patient age, multifocality, breast size, location of tumor in breast --- goal is clear margins in a normal looking breast
- Positive margins are being under-treated, **RE-EXCISE**
- Negative margins are being over-treated, **IF NO INK ON TUMOR SURFACE , NEED NOT RE-EXCISE**

Surgery of the primary breast cancer

In woman undergoing breast conserving surgery the minimum appropriate surgical margin is:

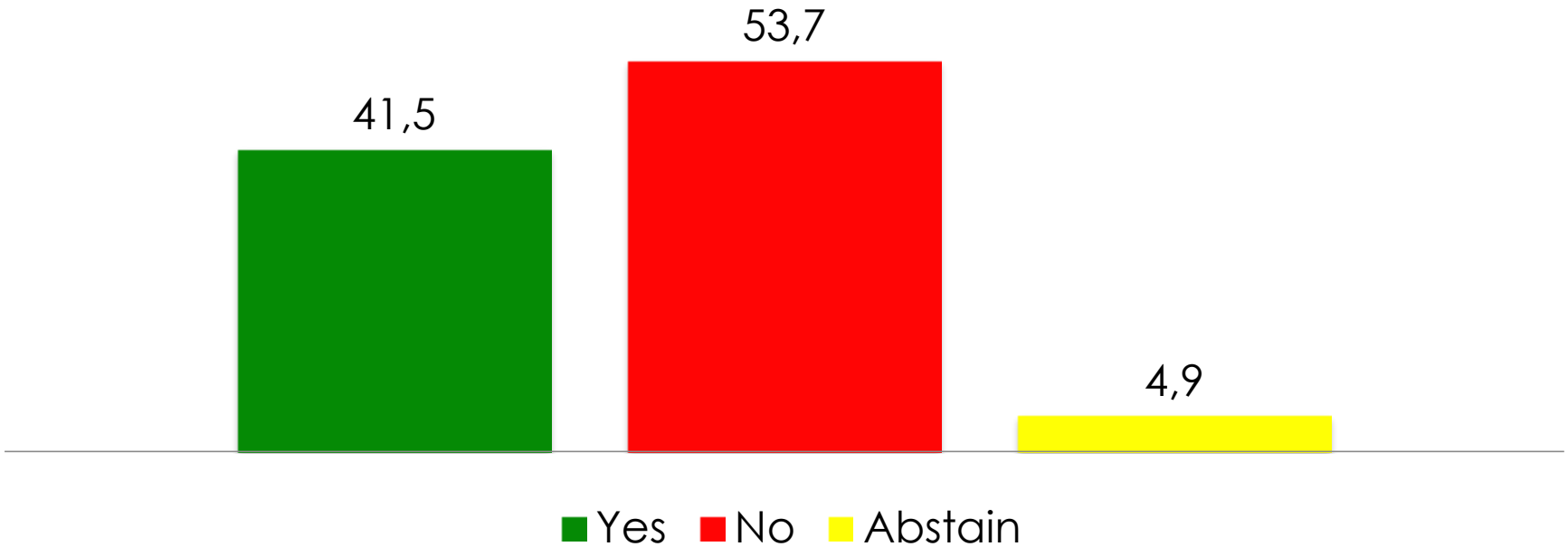
Important: In the following, if the panelist responded Yes then they had to Abstain the remaining questions…

Surgery of the primary breast cancer



Surgery of the primary breast cancer

Should the criteria that you have just identified be any different if there is DCIS at the margin (in a woman with invasive breast cancer)?



Comments

- **William Wood** stated that if there is DCIS at the ink then that is a positive margin still.
- **Monica Morrow** said that the vote in which 73% of respondents stated that the tumour is not on ink suggests that if you are taking out small specimens then there is not much role for things like oncoplastic surgery; this also minimizes excision and overall these factors are very positive for patients.

consensus

Surgery of the primary breast cancer

- Skin nipple sparing mastectomy is an acceptable treatment without RT.
- Skin nipple sparing mastectomy is an acceptable treatment in only if margin toward nipple is tumor free and immediate reconstruction planned.
- MRI should not be routine for patients with newly diagnosed disease (to assess decision on breast conserving surgery).
- In woman undergoing breast conserving surgery the minimum appropriate surgical margin is: “no ink on invasive tumor”.

In patients with macrometastasis in 1-2 sentinal lymph nodes, when completion of axillary dissection can safely be omitted?

THE LANCET Oncology

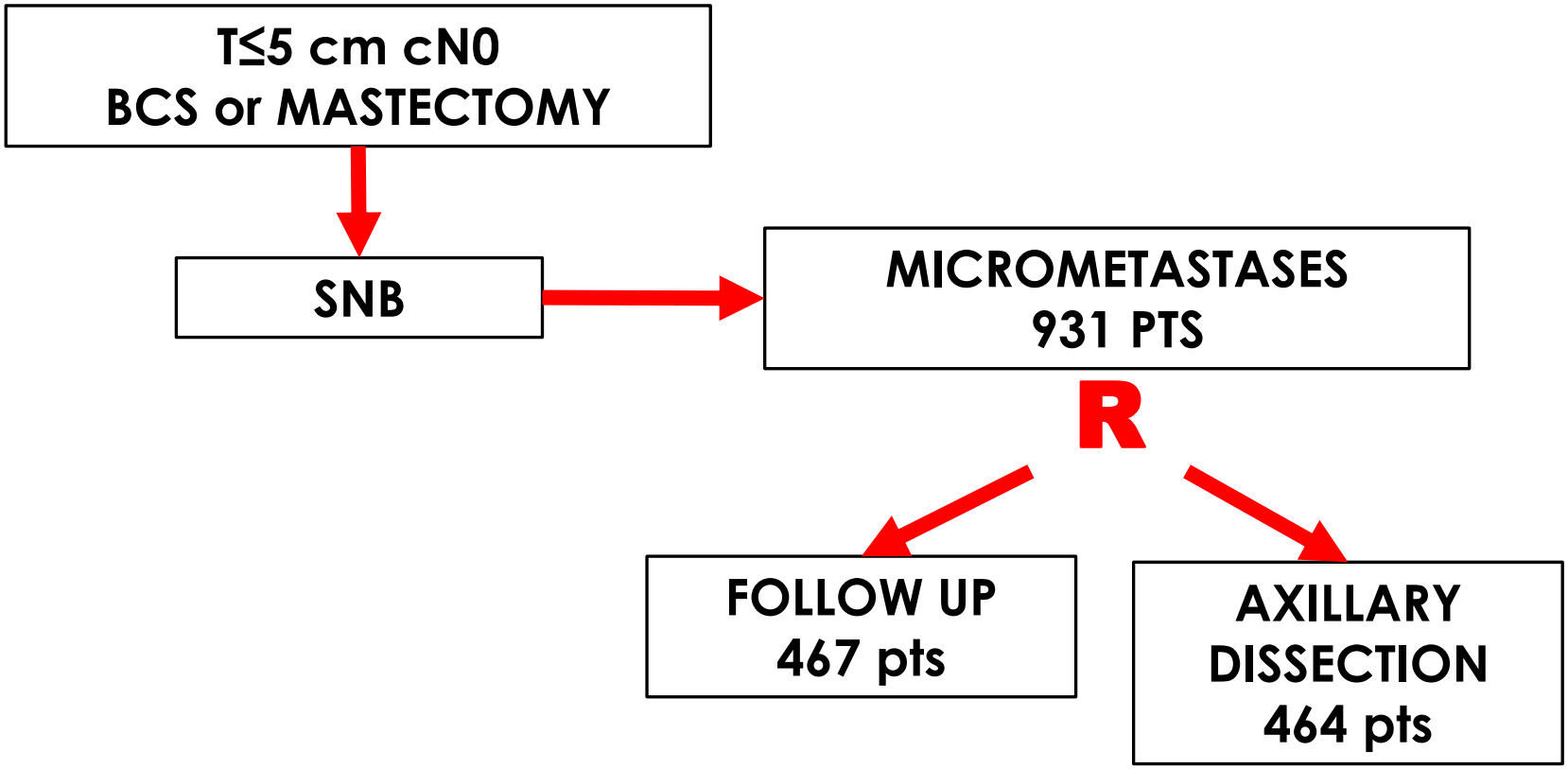
Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial

Viviana Galimberti, Bernard F Cole, Stefano Zurrida, Giuseppe Viale, Alberto Luini, Paolo Veronesi, Paola Baratella, Camelia Chifu, Manuela Sargenti, Mattia Intra, Oreste Gentilini, Mauro G Mastropasqua, Giovanni Mazzarol, Samuele Massarut, Jean-Rémi Garbay, Janez Zgajnar, Hanne Galatius, Angelo Recalcati, David Littlejohn, Monika Bamert, Marco Colleoni, Karen N Price, Meredith M Regan, Aron Goldhirsch, Alan S Coates, Richard D Gelber, Umberto Veronesi, for the International Breast Cancer Study Group Trial 23–01 investigators

Galimberti, V et al. The Lancet Oncology Martch 2013

IBCSG 23-01

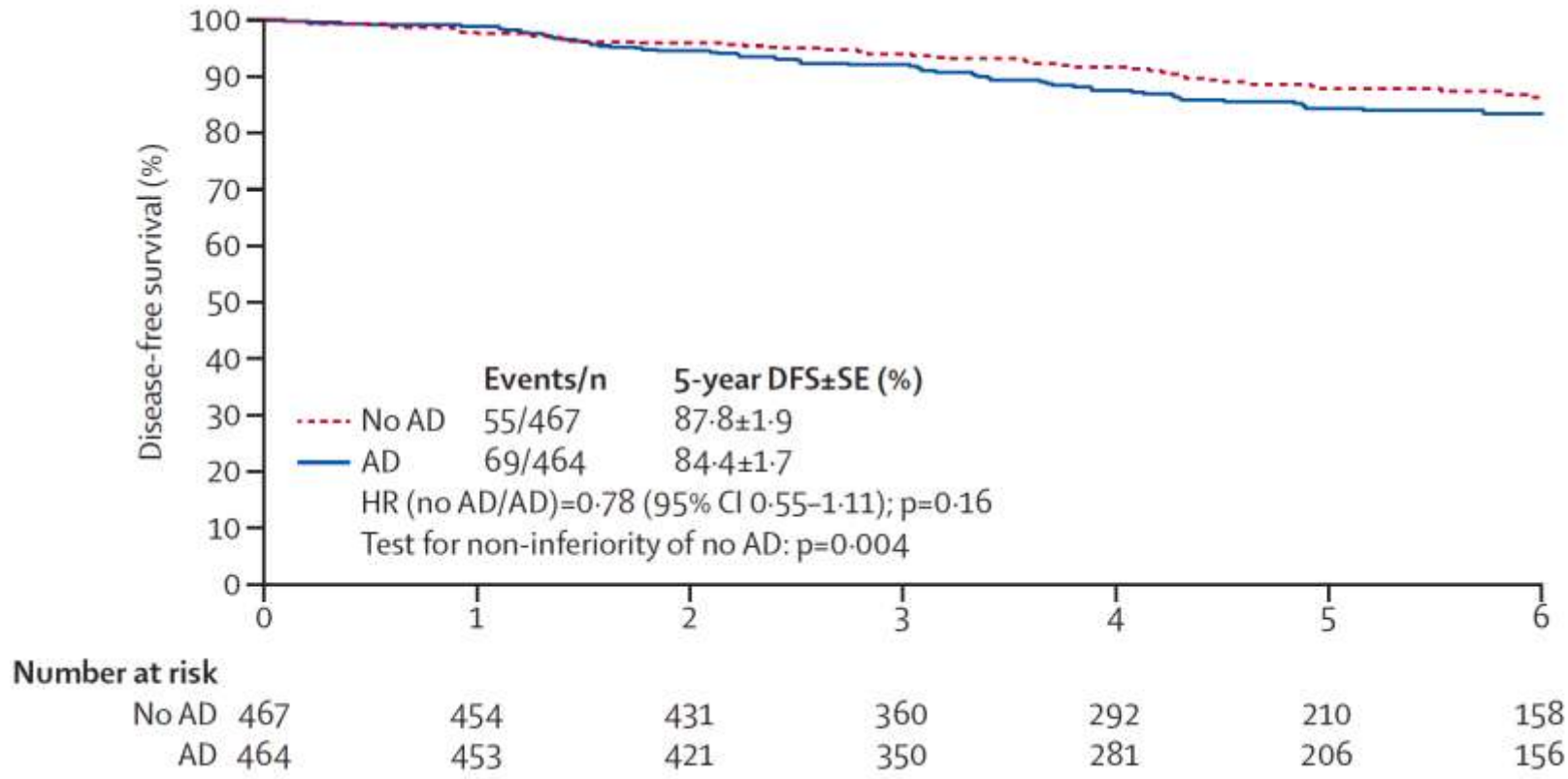
Apr 2001 – Feb 2010



Patients characteriics	AD (n=464)	No AD (n=467)	Total (n=931)
Local treatment			
Mastectomy	44 (9%)	42 (9%)	**86(9%)**
BCS	420 (91%)	425 (91%)	845 (91%)
RT on BCT			
No RT	10 (2%)	12 (3%)	22(3%)
Intraoperative only	79 (19%)	80 (19%)	**159(19%)**
Postoperative only	293 (70%	297 (70%)	590(70%)
Combination RT	36 (9%)	35 (8%)	71(8%)
Unspecified RT	2(<1%)	1(<1%)	3(<1%)
Systemic therapy			
Any systemic therapy	441 (95%)	451 (97%)	**892(96%)**
Hormonal therapy only	292 (63%)	315 (67%)	607(65%)
Chemotherapy only	42 (9%)	33 (7%)	75(8%)
Combination therapy	107 (23%)	103 (22%)	210(23%)

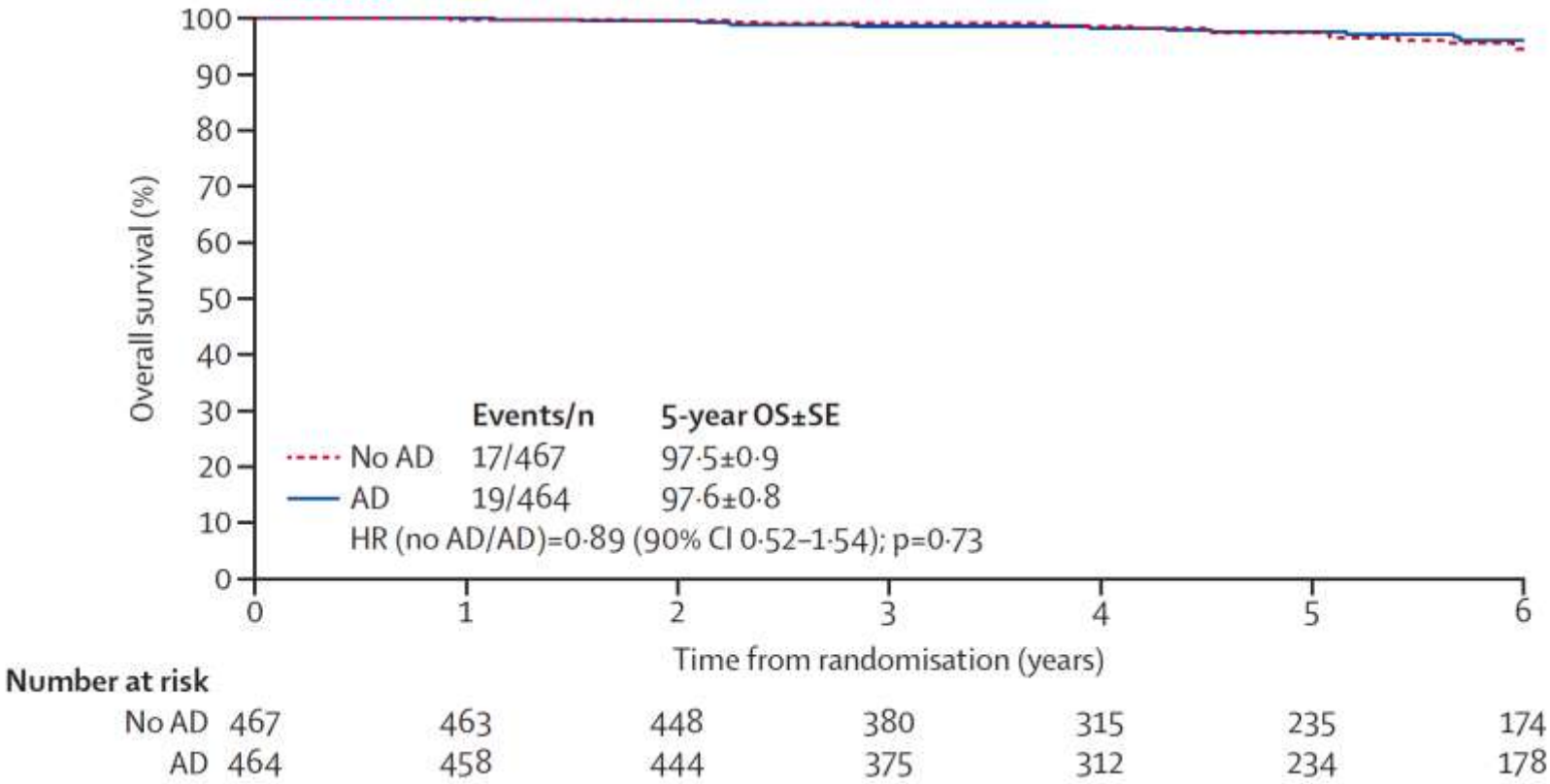
Galimberti, V et al. The Lancet Oncology Martch 2013

Disease-Free Survival



Galimberti, V et al. The Lancet Oncology Martch 2013

Overall Survival



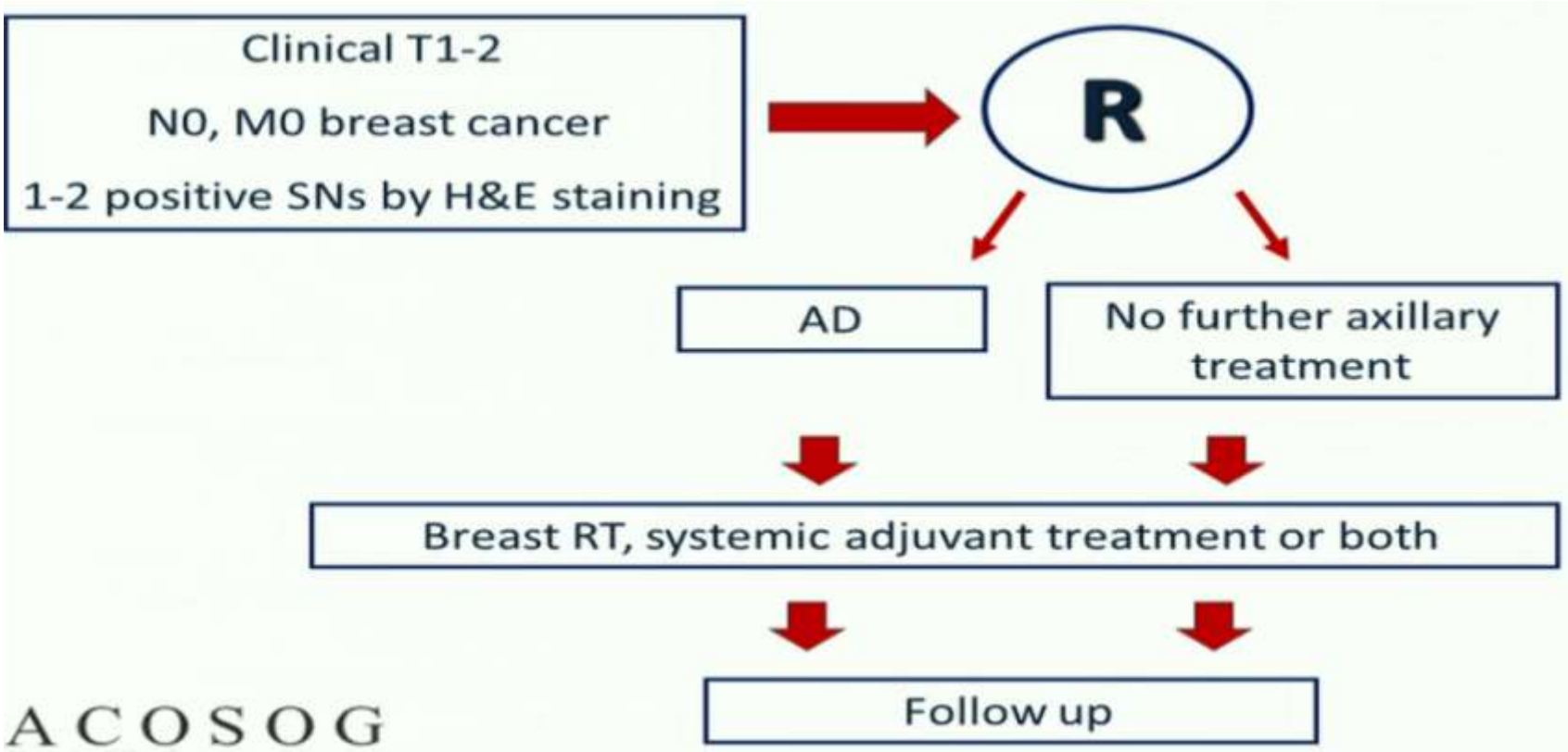
Galimberti, V et al. The Lancet Oncology Martch 2013

IBCSG 23-01 trial

- "Not giving AD to patients with 1 or more SN micrometastases has no adverse influence on DFS or OS"
- This is level 1 evidence in favour of the St Gallen 2011 recommendation that axillary dissection should not be performed if the sentinel node contains only micrometa

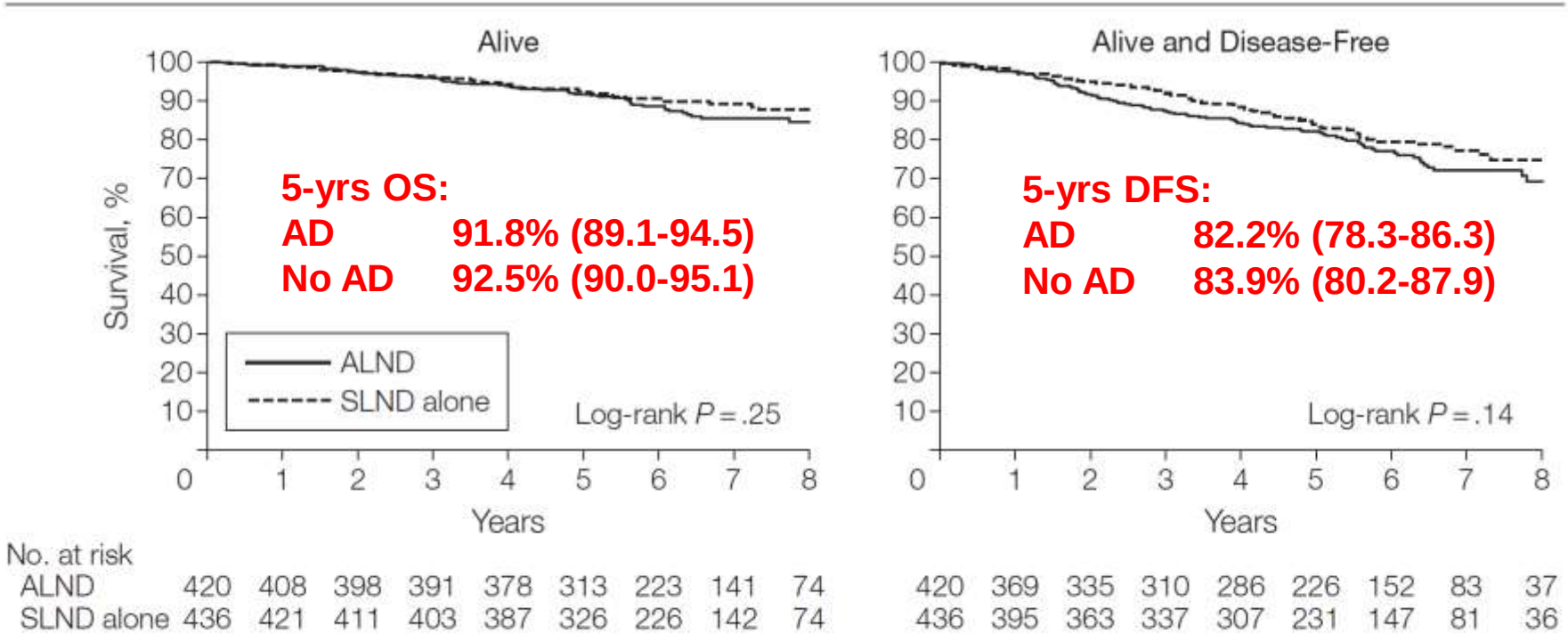
Trial Z0011

(closed 12/04 at n=891)



OS and DFS in trial Z0011

Survival of the ALND Group compared with SLND-Alone Group



No. at risk

ALND	420	408	398	391	378	313	223	141	74
SLND alone	436	421	411	403	387	326	226	142	74

ALND	420	369	335	310	286	226	152	83	37
SLND alone	436	395	363	337	307	231	147	81	36

ALND indicates axillary lymph node dissection; SLND, sentinel lymph node dissection.

Giuliano AE et al. JAMA. 2011;305(6):569-575

Z0011 Conclusion

"it is time to abandon AD in early BC pts with a positive SN provided they receive systemic adjuvant treatment and whole breast RT"

Criticisms of Z0011

Criticisms

- Trial closed recruiting only half projected number of pts
- Might not have power to detect a small difference in outcomes betwen groups
- Axillary recurrence rate in the no AD arm double that in the AD arm
- Non- inferiority criterion too lax (5 yr survival in the no AD arm assumed not less than 75% of that in the AD arm)
- No AD = no information on any additional axillary involvement that may change adjuvant treatment

Rebuttals

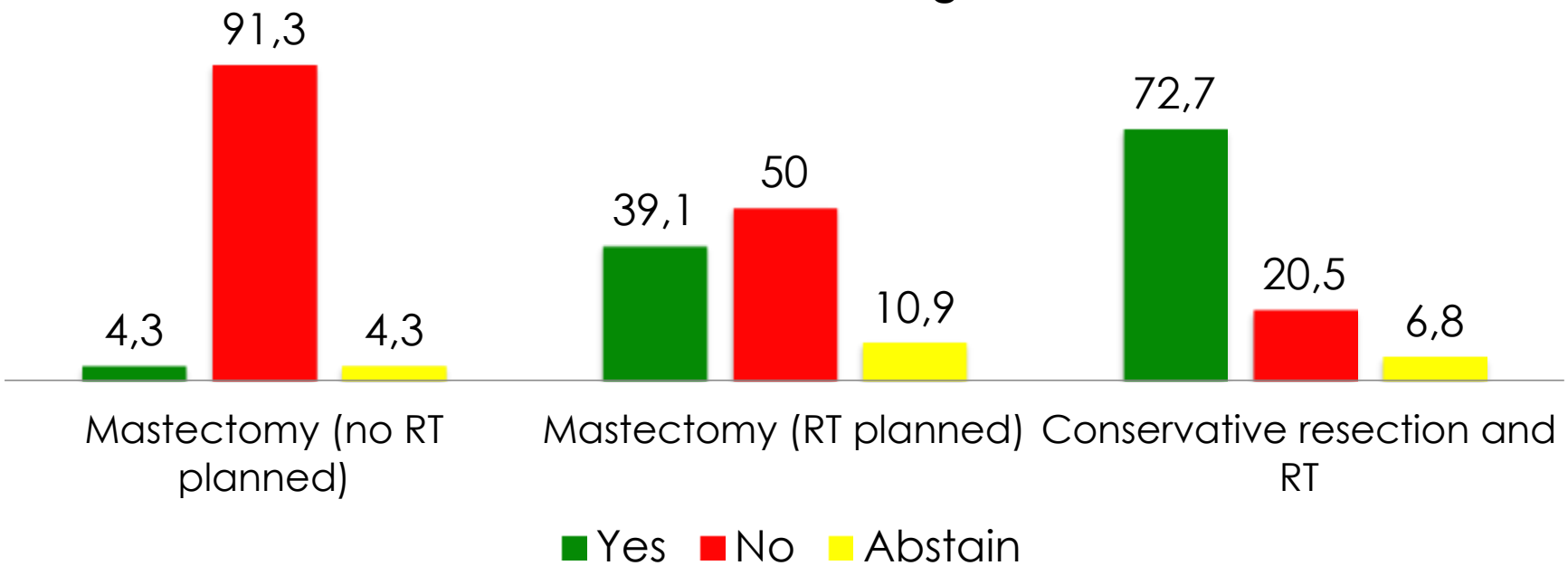
- No difference in 5-yr OS
- No difference in 5-yr DFS
- Excelent OS and DFS in no AD group
- In fact OS and DFS non signifiticantly better in no AD arm
- Low rate of axillary disease in no AD arm
- Data indicate that complete axillary information almost never changes adjuvant treatment

Take Home Massage

- For most patients with early breast cancer and a clinically negative axilla, a positive SN should not be futher treated
- Caution: the desicion should continue to consider all the relevant factors including patient age, comorbidities, and also patient preference

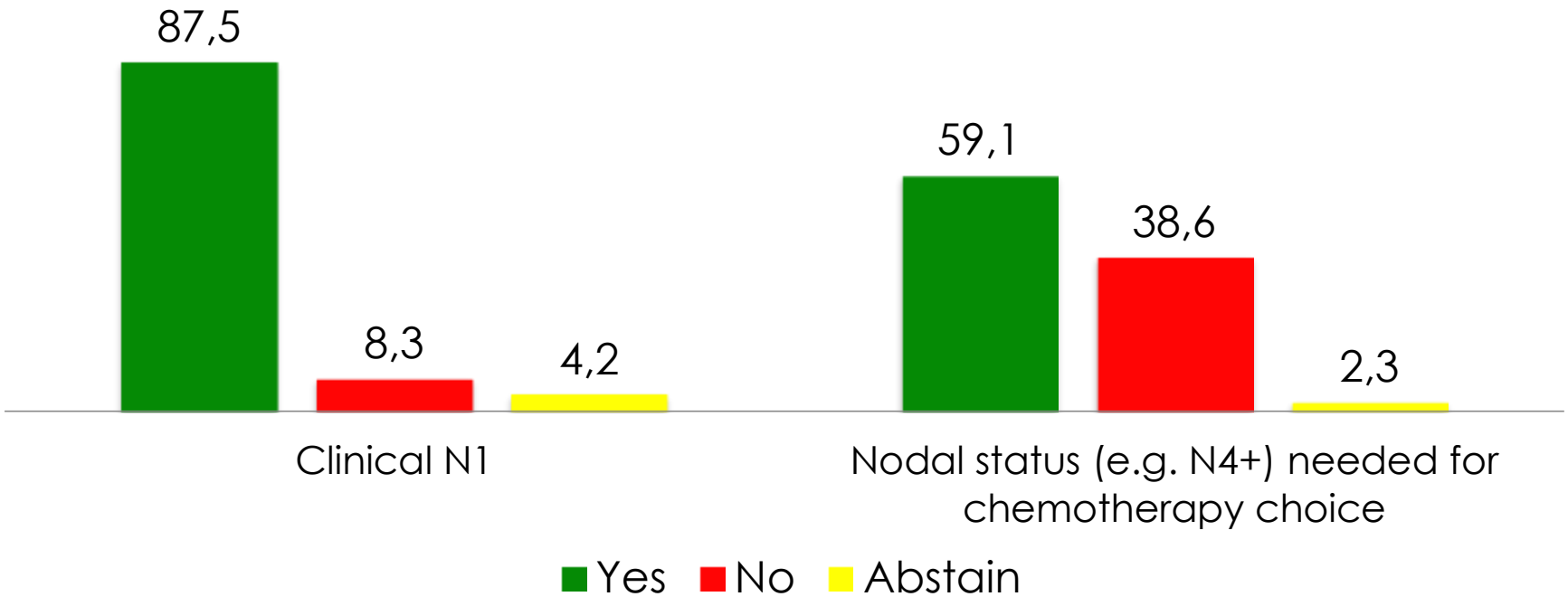
Surgery of the axilla

In patients with macrometastasis in 1-2 sentinal lymph nodes, completion of axillary dissection can safely be omitted following:



Surgery of the axilla

In patients otherwise undergoing breast conserving surgery, completion of axillary dissection is necessary if:



Comments

Monica Morrow stated that it is very encouraging to see much greater acceptance of lack of dissection for one or two macrometastases in patients having breast conservation where the data actually exist. To address another point on young women with ER- tumours, she said that she was unable to find any data that says age is a predictor of nodal failure; ER negativity is actually associated with a lower nodal disease burden. We also need to be careful about extrapolating the data beyond what we know is safe and we really have no data addressing any of the circumstance of clinical positive nodes or three or more nodes that are associated with heavy disease burdens. Furthermore, however many sentinel nodes either turn blue or hot is how many need to be removed; the eligibility criteria in study Z11 does absolutely not mean you need to remove three nodes every time. What is important is that you stick your hands in there and feel to make sure you are not leaving behind gross nodal disease, bearing in mind that a lot of patients have only one sentinel node.

consensus

Surgery of the axilla

- In patients with macrometastasis in 1-2 sentinal lymph nodes, completion of axillary dissection can safely be omitted following BCT and RT.

- In patients otherwise undergoing breast conserving surgery, completion of axillary dissection is necessary if:
  - There is clinical N1 disease,
  - If nodal status needed for chemotherapy choice.

Conference Topic

Radiation therapy

Is there a group not requiring radiotherapy as part of Breast Conserving Therapy (BCT)?

Radiotherapy: Conserved Breast Irradiation

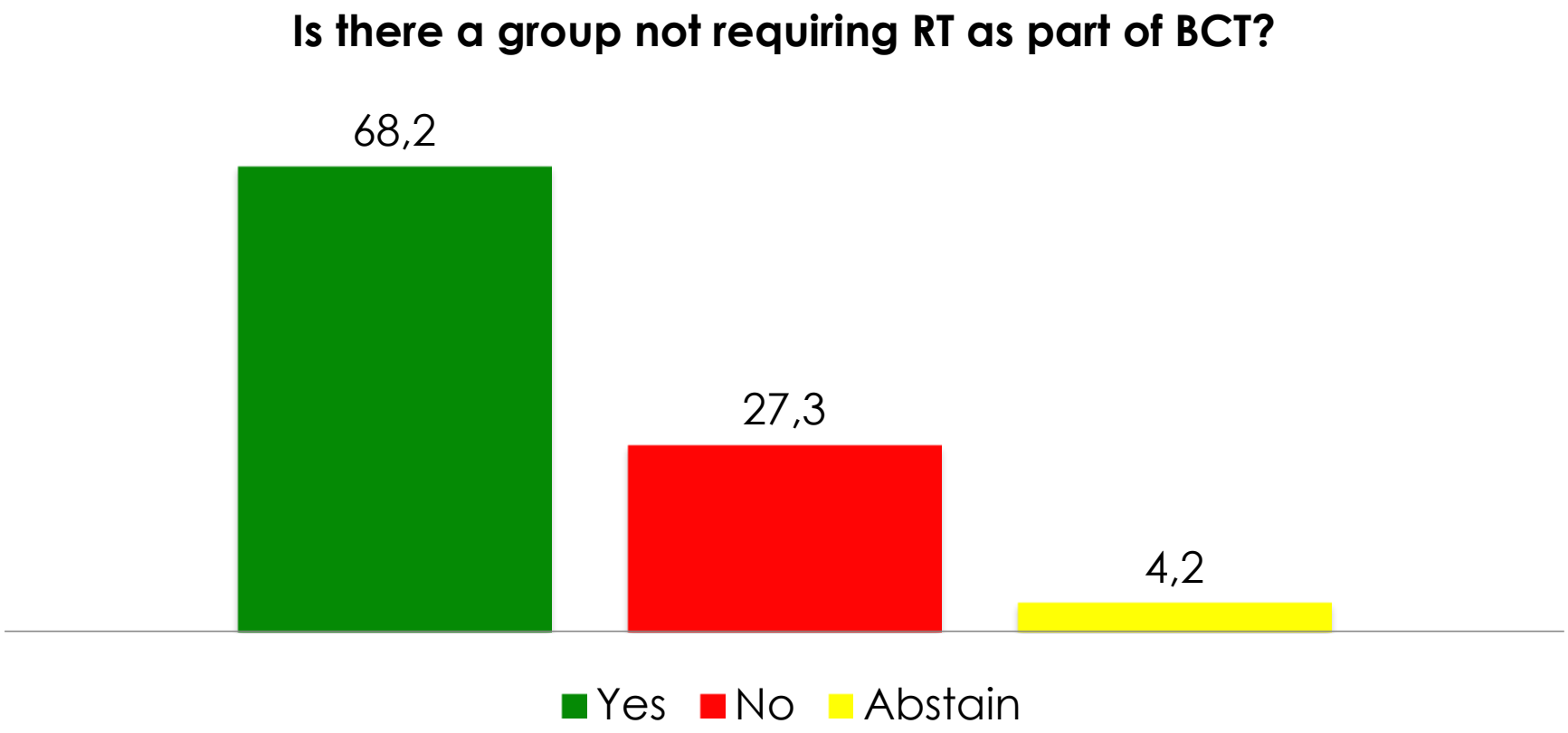
- **>70 y Stage I, ER+, if able to take TMX, RT may be omitted**
  - TAM vs. Tam+RT
  - FU: 10,5 years

	TAM	Tam+RT
Loco-regional recurrence	%9	%2
10y Mastectomy free survival	%96	%98
10 yr DMFS	%95	%93

DMFS: Distant metastatic free survival

Hughes, ASCO 2010

Radiotherapy: Conserved Breast Irradiation



Should short course RT (e.g. 40 Gy in 15 fractions) be offered as standart?

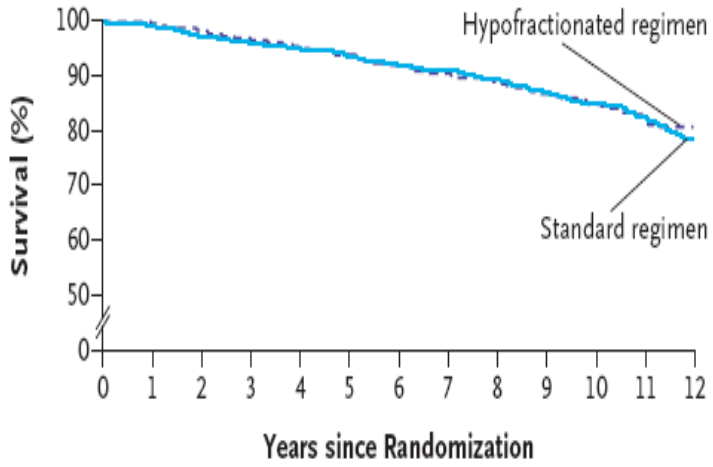
Hypofraction RT Trials

	Canada	Start A UK *	Start B UK
Number of pts	1234	2236	2215
Med. Follow up	12 yr	9,3 yr	9,9 yr
Arms (Gy x fr number)	2x25/5 wk 2,66x16/3 wk	2x25 /5 wk 3x13 /5 wk 3,2x13/5 wk	2x25/5 wk 2,66x15/3 wk

*Trial to determine α/β ratio

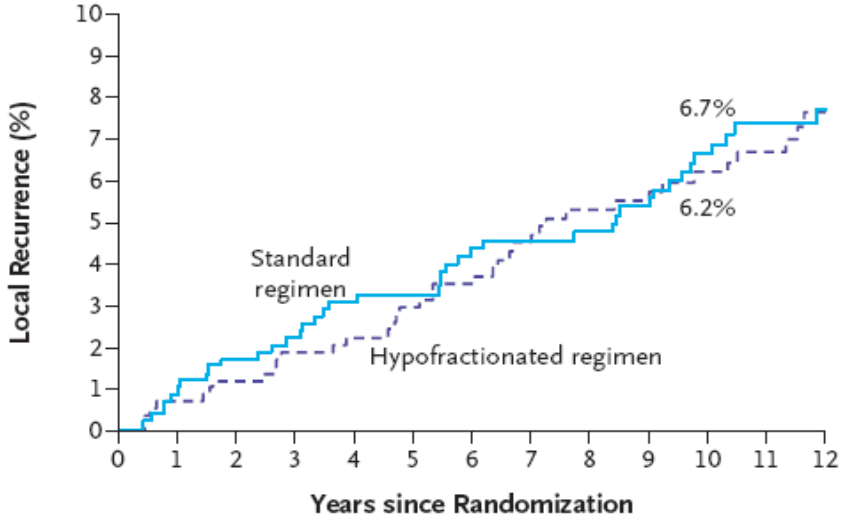
Harris, SGBCC, 2013

Radiotherapy: Conserved Breast Irradiation



No. at Risk

Standard regimen	612	606	594	583	573	559	535	519	505	487	453	355	242
Hypofractionated regimen	622	617	605	592	576	562	539	517	495	482	455	369	241



No. at Risk

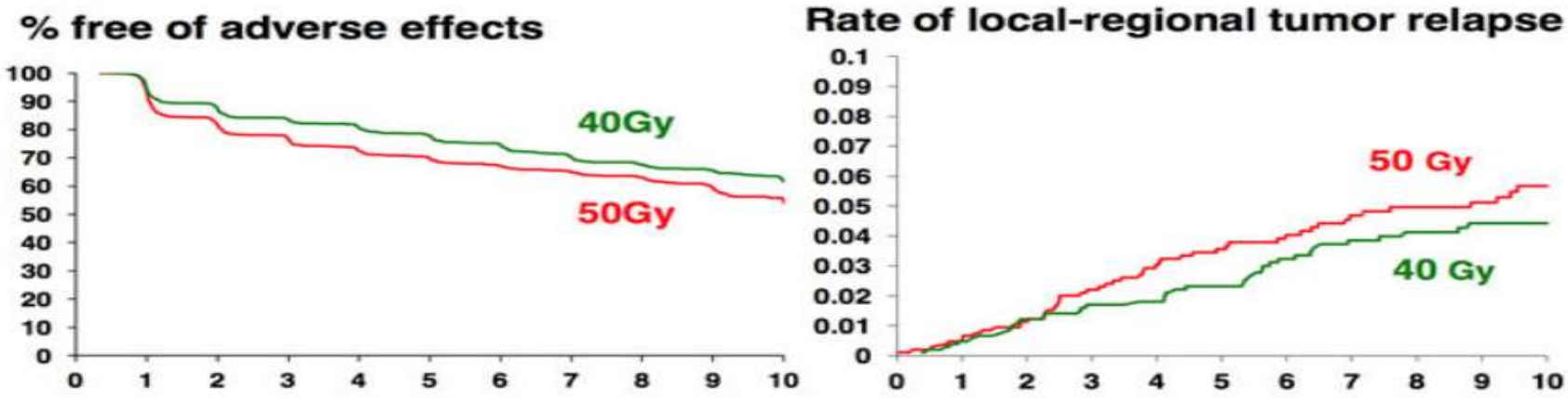
Standard regimen	612	597	578	562	550	553	499	485	470	449	410	317	218
Hypofractionated regimen	622	609	592	569	548	524	500	472	447	430	406	330	214

Whelan, NEJM, 2010

Radiotherapy: Conserved Breast Irradiation

Trial B: Results

5



	Hazard Ratio (95%CI)
40Gy vs. 50Gy	0.77 (0.66-0.89)

	Hazard Ratio (95%CI)
40Gy vs. 50Gy	0.77 (0.51 – 1.16)

Yarnold, SABC 2012

Radiotherapy: Conserved Breast Irradiation

	Canada, %	START B, %
ER –	27	12
Grade 3	19	23
Age < 50	25	21
Boost	0	43
Nodal RT	0	7
Chemo	11	22

Harris, SGBCC, 2013

Radiotherapy: Conserved Breast Irradiation

ASTRO 2011 Hipofx Breast RT Guideline	
Age/Stage	≥ 50 y, T1-2
Surgery	Breast Conserving Surgery
Chemotherapy	-
Fractionation	2,66 Gy x 16
Heart in feld	0
Boost	No aggrement
Dose Homogeneity	≤ 7 %

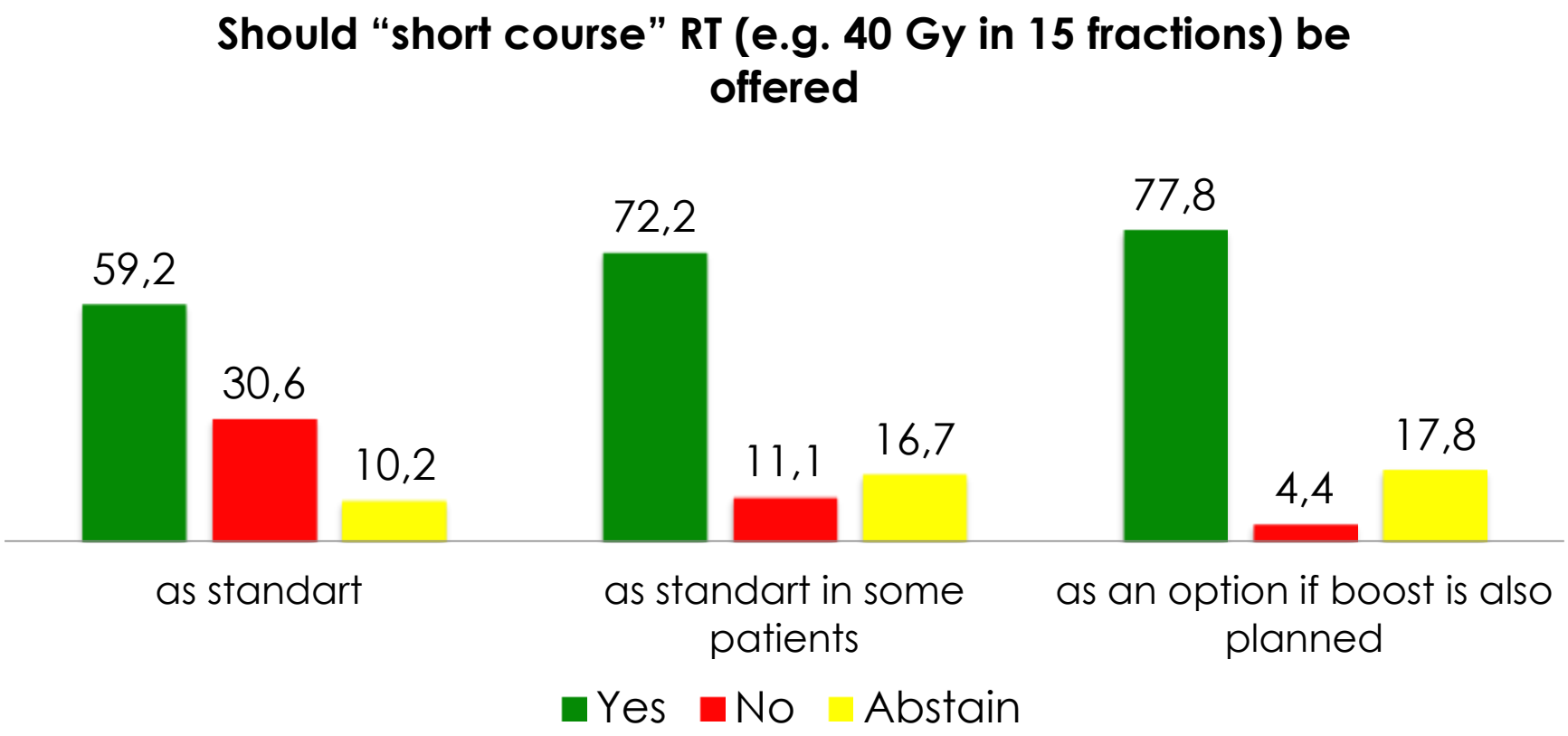
Smith, IJROBP, 2011

Radiotherapy: Conserved Breast Irradiation

New DFCI / BWH Approach	
Age/Stage	≥ 50 y, DCIS ≥ 60, Tangents only
Surgery	Breast conserving surgery
Chemotherapy	OK
Fractionation	2,66 Gy x 16
Heart in feld	0
Boost	2,5 Gy x 2-4
DoseHomogeneity	≤ 7 %

Harris, SGBCC, 2013

Radiotherapy: Conserved Breast Irradiation



Comments

- **Jay Harris** stated that, with regard to the first point, it is very clear that in patients who are younger, radiation after breast conserving surgery improves long-term survival but as patients age the survival advantage decreases due to competing risks and so the answer to the first question is clearly yes, mostly predicated on age and comorbidities. We've just seen such good data for short course radiotherapy and it is likely that over time more of us will say this is standard therapy but in the US we are still not quite there.
- **Felix Sedmayer** added that while this may be common practice in the US this is quite the opposite of the situation in Europe, as reflected by most European guidelines. Not a single cohort has been identified up until now where radiotherapy can be omitted safely without compromising local tumour control. These patients with low risk are the focus of reduced radiotherapy.

Following breast conserving surgery Partial Breast Irradiation (PBI) may be used as the definitive irradiation without any external beam therapy (ASTRO/ESTRO group)?

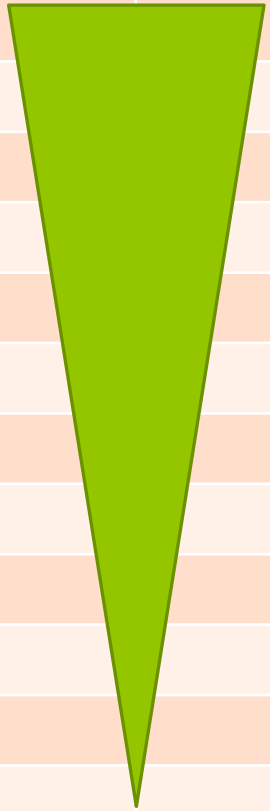
PBI Clinical Results

Trial	Med. FU	Local Relaps %
Budapest [HDR 5,2 Gy x 7 fr / 4 days or 50 Gy é]	120 months	5,5 %
Targit [50KeV, 20 Gy at surface of the applicator 5-7Gy at 1cm]	29 months	3,3 %
ELIOT [electron, 21 Gy to %90 isodose line]	63 months	5,3 %
ELIOT out trial	60 months	6 %
Mamosite Registry [3,4 Gy to 1 cm x 10 fr]	42 months	3,8 %

Orecchia, SGBCC, 2013

5-y Local Relapse Rates after BCS+WBI

NSABP B-06	(1976-1984)	14,3
Uppsala-Örebro	(1981-1988)	8,5
St. George's London	(1981-1990)	13
CRC, UK	(1981-1990)	19,7
Ontario COG	(1984-1989)	11
SCTBG	(1985-1991)	5,8
INT Milan 3	(1987-1989)	5,8
NSABP B-21	(1989-1998)	2,8
Swedish BCG 91-RT	1991-1997	4
Holli et al	1990-1995	6,3
Fyles et al	1992-2000	0,6
ABCSG study 8	1996-2004	0,4



Orecchia, SGBCC, 2013

TARGIT: Update at SABCS (December 2012)

- 5-year cumulative risk (29 months median follow up)

	Targit	EBRT	p
IBR%	3.3 (23)	1.3(11)	0.042
All LR%	8.2 (69)	5.7 (48)	NS
Total Deaths%	3.9 (37)	5.3 (51)	NS

- Intention to treatment
- EBRT in unfavourable pathology
- Over 60% in the "suitable" ASTRO group

Orecchia, SGBCC, 2013

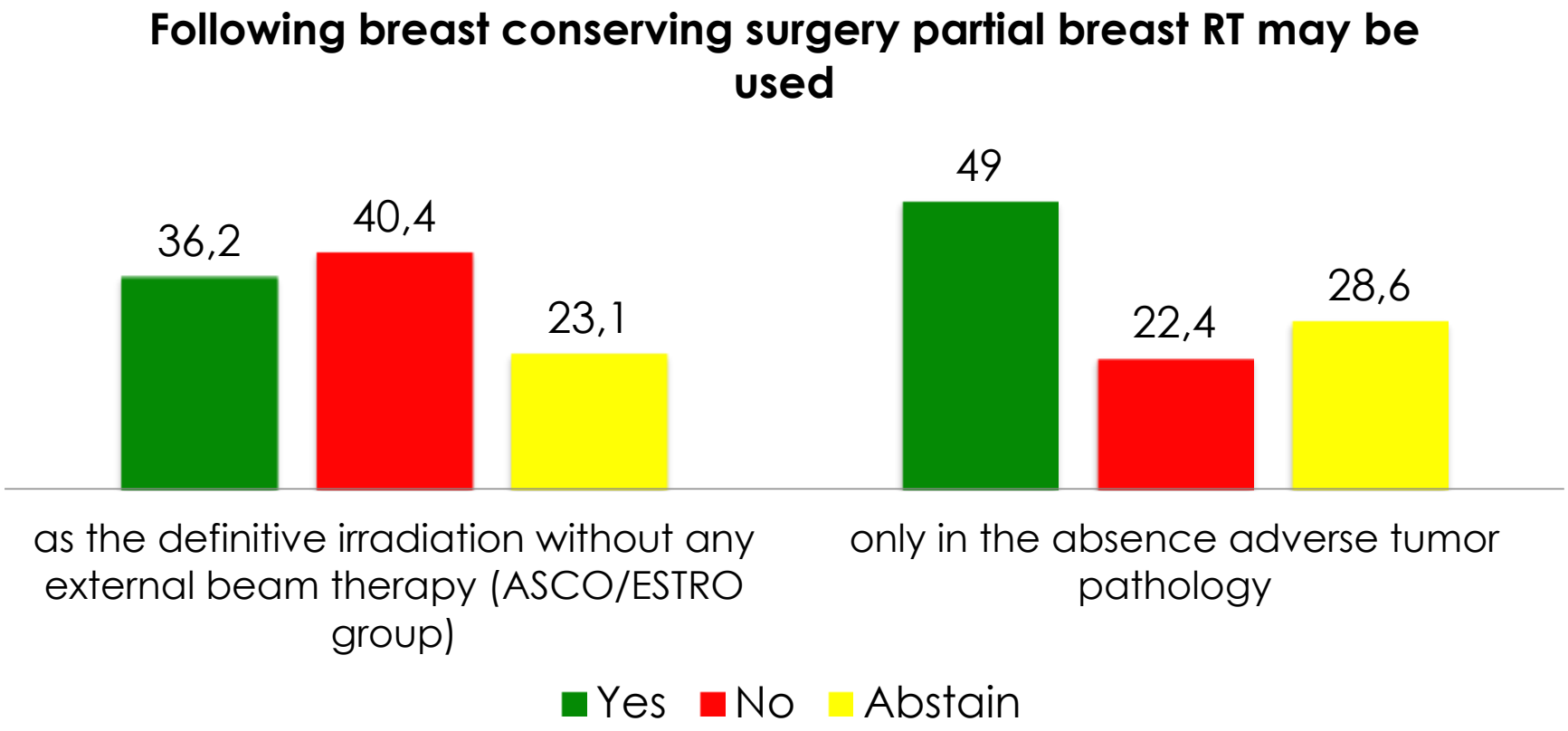
	ASTRO guidelines		
	Suitable	Cautionary	Unsuitable
Patient factors			
Age, years	≥60	50—59	<50
BRCA1/2 mutation	Absent	Absent	Present
Pathologic factors			
Tumor size, cm	≤2	2.1—3.0	>3
pT	pT1	pT0 or pT2	pT3—pT4
Margins	Negative	Close	Positive
Grade	Any	Any	Any
LVI	No	Limited/focal	Extensive
ER status	Positive	Negative	Any
Multicentricity	Uncentric	Unicentric	Present
Multifocality	Unifocal	Unifocal	Multifocal
Histology	Invasive ductal*	Invasive lobular	Any
Pure DCIS	Not allowed	≤3 cm	>3 cm
EIC	Not allowed	≤3 cm	>3 cm
Nodal factors			
Nodal stage	pN0 (i^-,i^+)	pN0 (i^-,i^+)	pN1, pN2, pN3
Nodal surgery	SNB or ALND	SNB or ALND	Not performed
Treatment factors			
Neoadjuvant therapy	Not allowed	Not allowed	Yes

Table 3 Five-year clinical outcomes for breast cancer patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statement

	ASTRO consensus statement						
	Suitable		Cautionary		Unsuitable		
Patients	294		691		812		
Person-years	1,009		2,416		2,837		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
Ipsilateral breast tumor recurrence	3	1.5	21	4.4	50	8.8	0.0003
Regional lymph node failure	3	1.5	9	1.9	6	1.1	0.55
Distant metastases	3	1.5	8	1.7	22	3.9	0.047
Breast cancer related event	14	6.9	46	9.5	87	15.3	0.0025
Progression free survival	17	91.6	58	88.0	109	80.8	0.0005
Cause-specific survival	2	99.1	7	98.7	22	96.5	0.026
Overall survival	3	98.6	13	97.5	30	95.2	0.039

Leonardi, IJROBP, 2012

RT: Partial Breast Irradiation



Comments

- **William Wood** admitted to having voted no, stating that it will be 15 years before we know the results of this technique, so he is personally not enthusiastic about it. Obviously we have good short term data and in the short term this is fine.
- **Andrew Tutt** referred to a presentation from Friday on the big variation in the way partial breast radiotherapy can be delivered both in terms of dose fractionation and volume of tissue irradiated and he thought that the answers to the questions above could be applied to one of those techniques. So he thought that a yes to that question could lead people to conclude that one of the available techniques is perfectly acceptable whereas the data are different and, for some of the techniques, the data are quite clearly inferior.

Comments

- **Jay Harris** added that, in the US there is a lot of controversy about how safe accelerated partial breast irradiation is using external beam radiation. Within the clinical trial the results seem to be good but recently that in a Canadian trial has seen a lot of adverse cosmetic outcomes pretty early on and the doses and volumes are very similar and so he can see why people are not completely comfortable with this approach.

Should postmastectomy RT be standard for patients with:

N+ >3 LN?

N+ 1-3 LN; all patients?

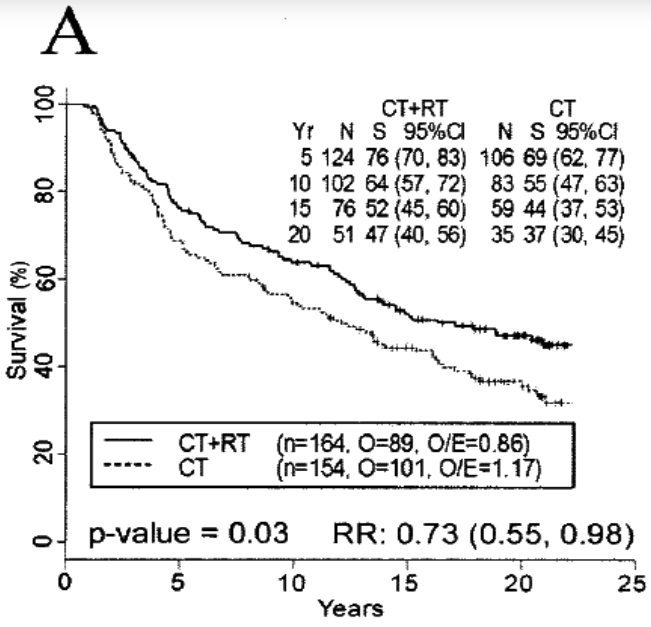
N+ 1-3 LN; with adverse pathology?

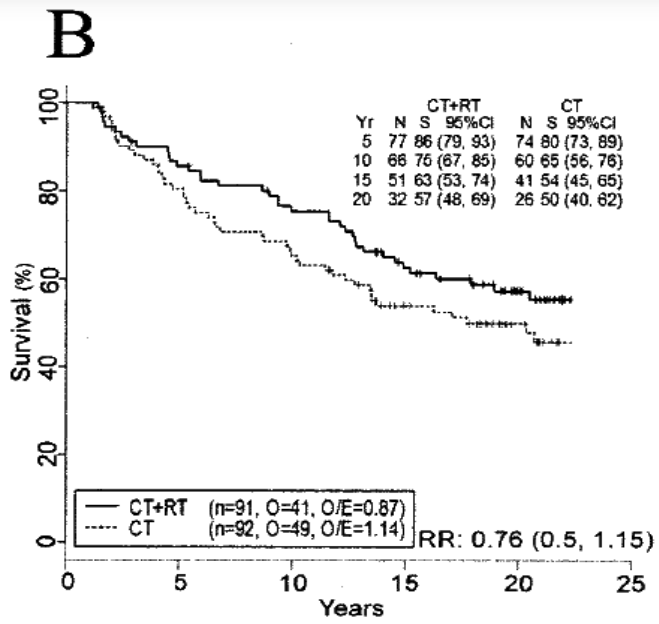
N+ 1-3 LN; young age (<40 y)?

Radiotherapy: Postmastectomy

N+ 1-3 LN; all patients

British-Columbia Trial (J Natl Cancer Inst 2005)	318 pLN+ Premeno-pausal patients status postmodified radical mastectomy	CMF chemo alone vs. chemo + RT	20 Years	RT reduced LRF (26→10%), and improved breast ca-specific survival (38→53%), and OS (37→47%)	Median 11 LN sampled

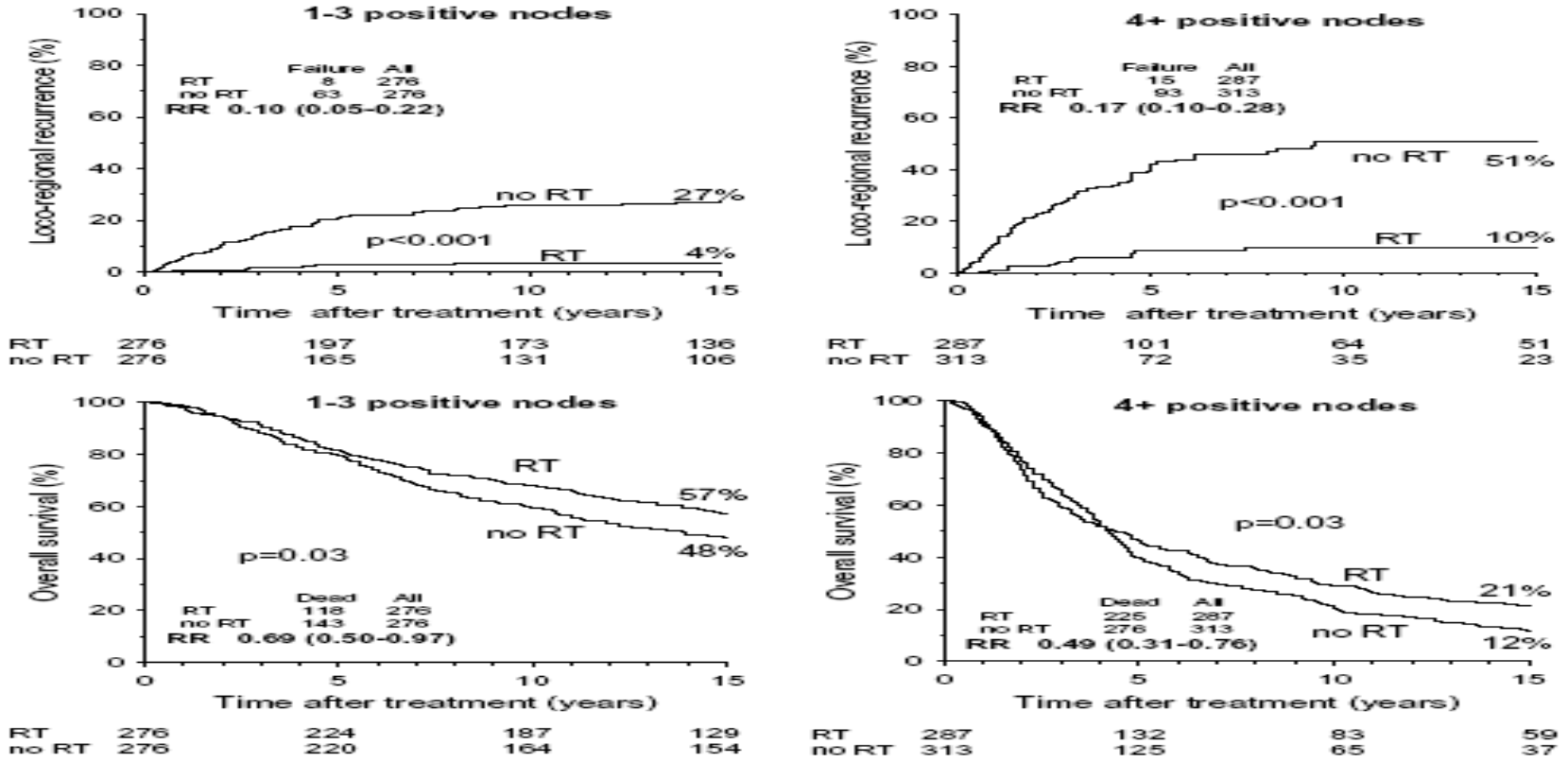




Radiotherapy: Postmastectomy

N+ 1-3 LN; all patients

DBCG 82 b&c postmastectomy radiotherapy



Overgaard, RO, 2007

RT: Postmastectomy

N+ 1-3 LN; with adverse pathology

	5-year local recurrence risk (%) in trials of:	
	(b) RT after mastectomy and AC (node-positive)	
	RT versus control	Absolute reduction (SE)
Tumour grade		
Well differentiated	4 vs 22	18 (3)
Moderately differentiated	4 vs 30	26 (2)
Poorly differentiated	6 vs 40	34 (4)

EBCTCG, 2005

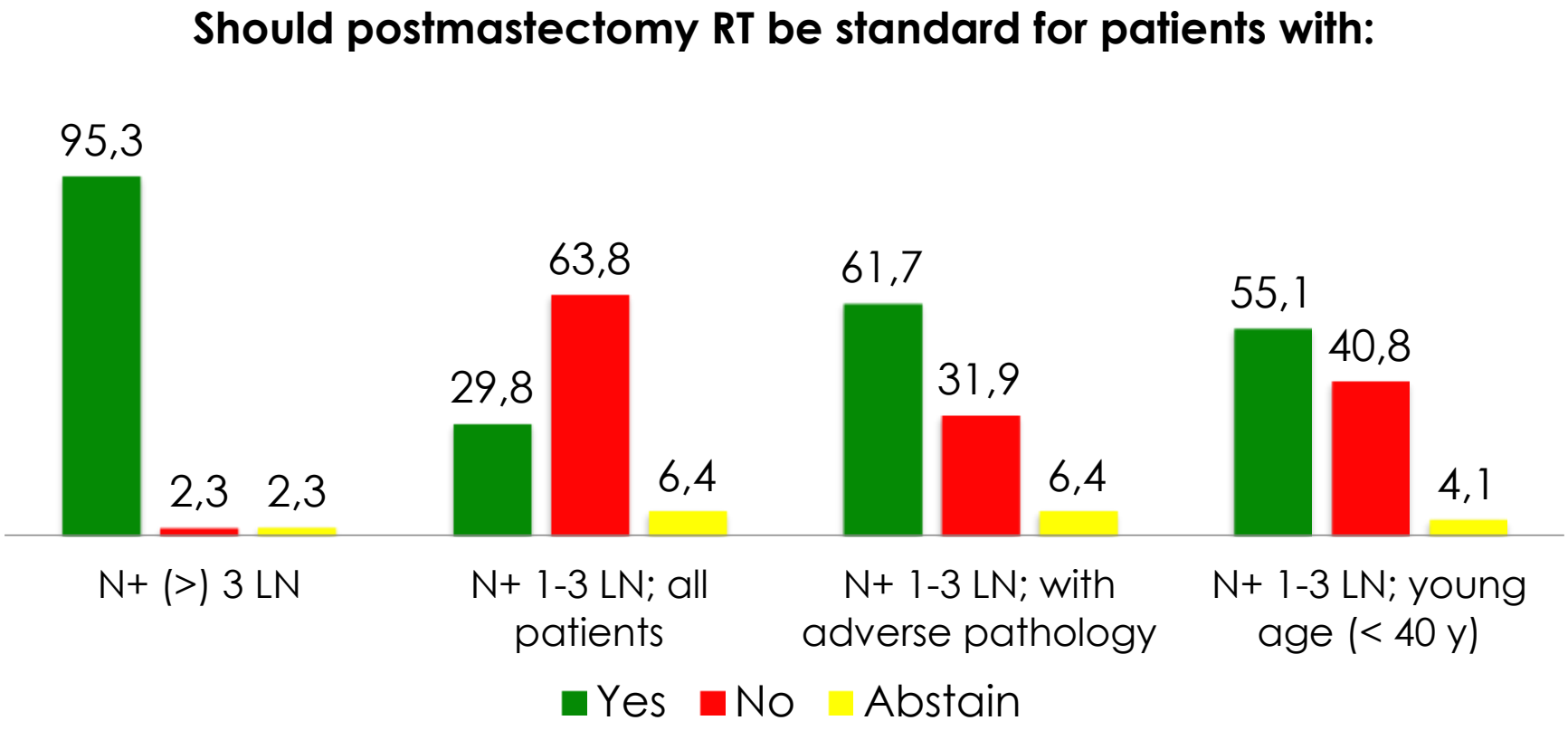
RT: Postmastectomy

N+ 1-3 LN; young age (< 40 y)

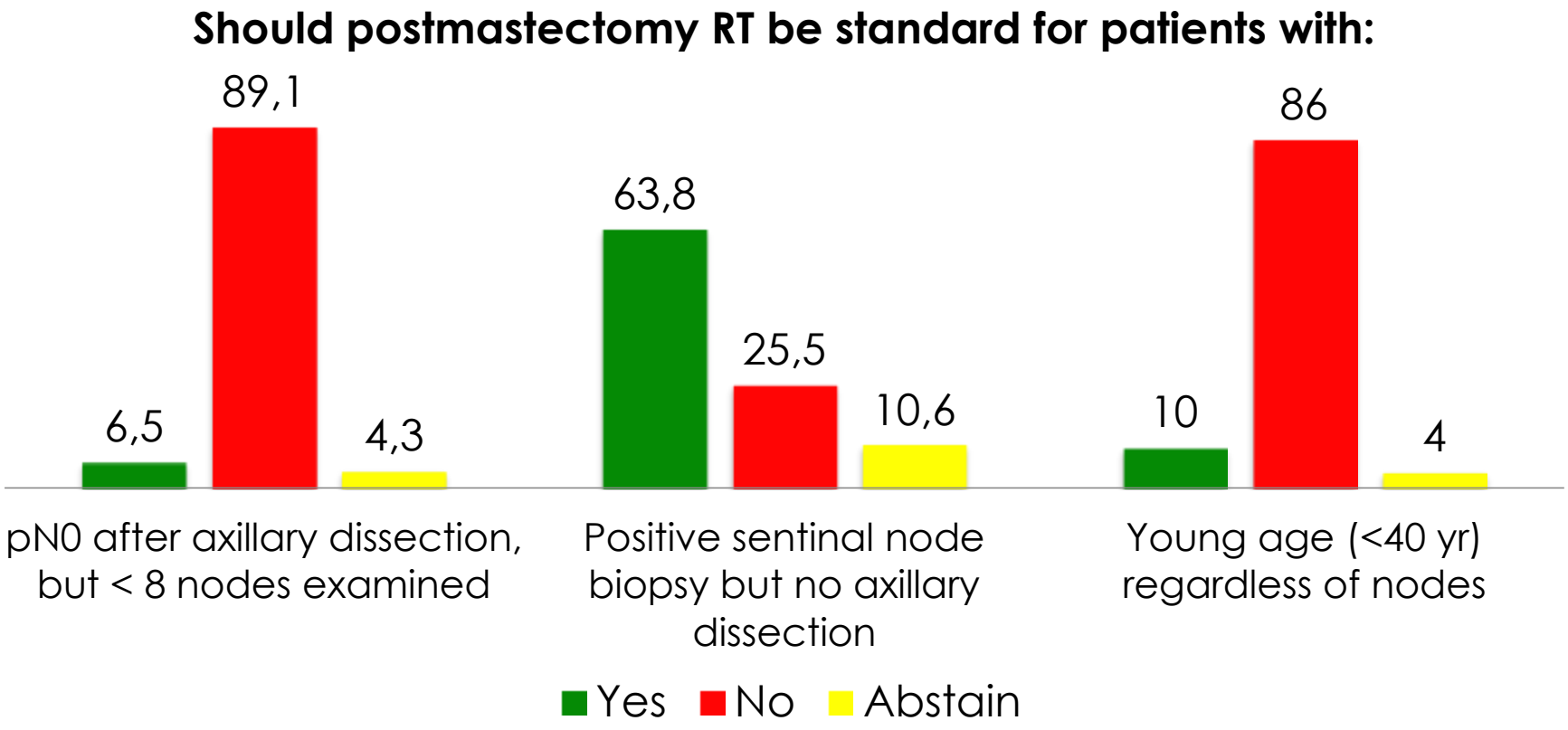
	(b) RT after mastectomy and AC (node-positive)	
	RT versus control	Absolute reduction (SE)
Age (years)		
<50	6 vs 23	17 (1)
50–59	6 vs 24	18 (2)
60–69	5 vs 23	18 (2)
⩾70	..	..

EBCTCG, 2005

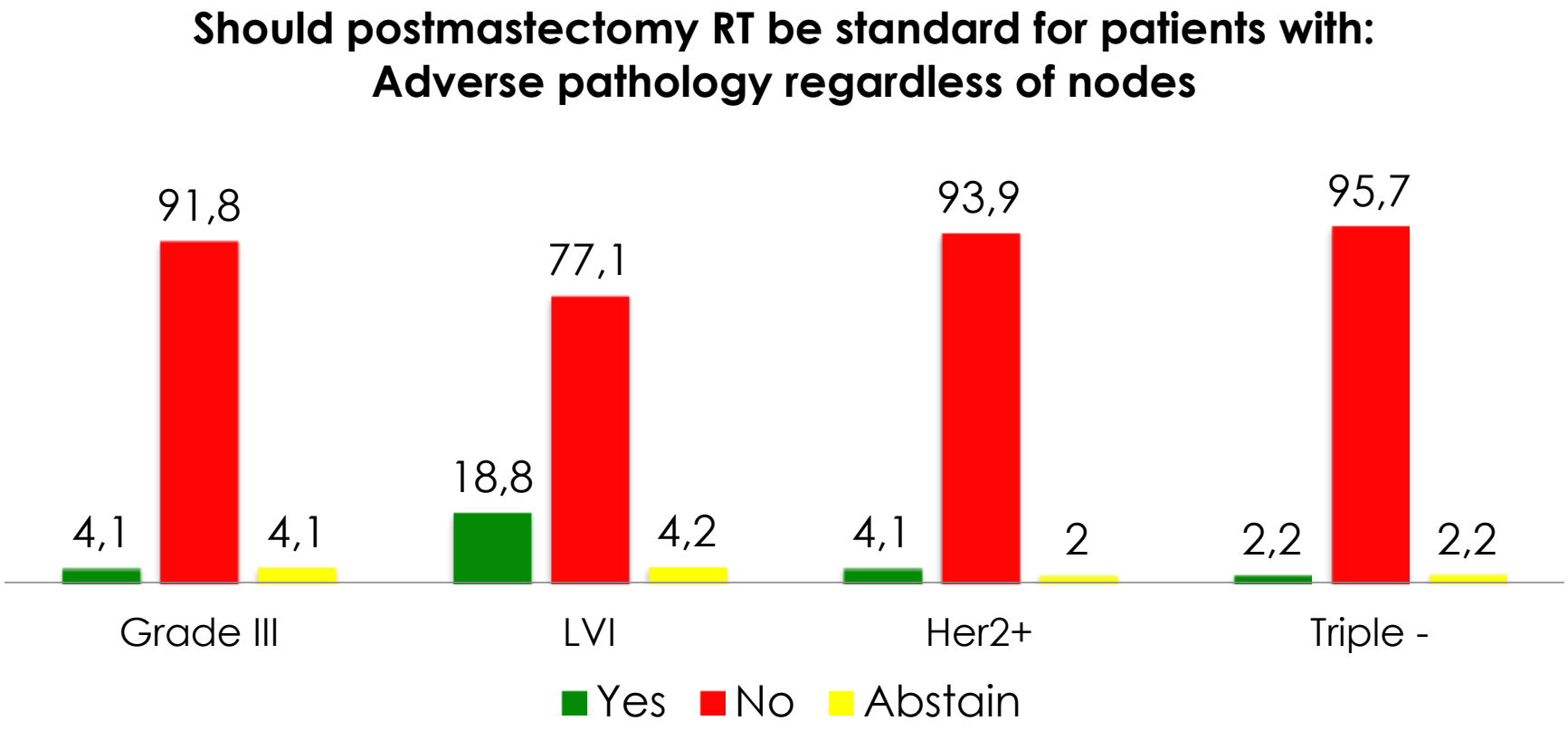
RT: Postmastectomy



RT: Postmastectomy

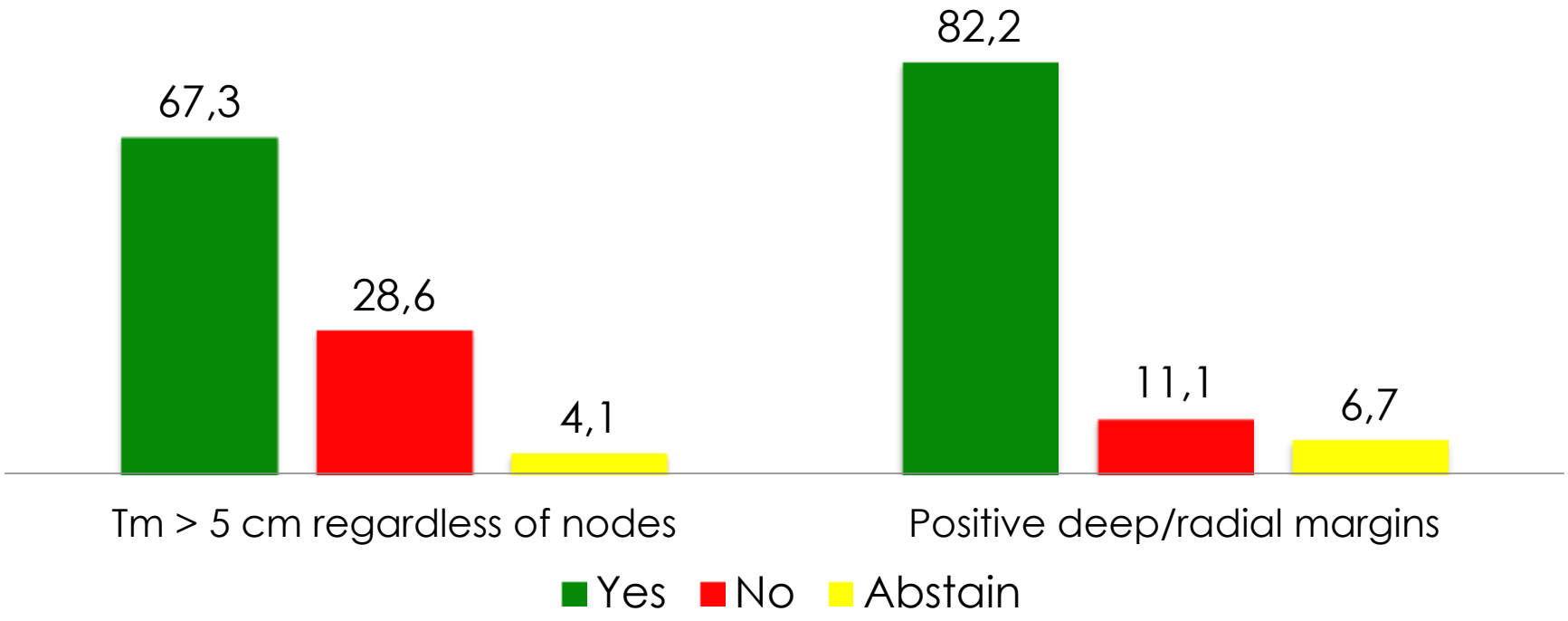


RT: Postmastectomy



RT: Postmastectomy

Should postmastectomy RT be standard for patients with:



Comments

- **Monica Morrow** remarked that the other thing that is different today is that women undergoing mastectomy with one to three nodes are not the same as women who underwent mastectomy in the trials in the pre-screening era. Now we have a have a lot of women who choose to have mastectomy for 5 mm cancers with a very low nodal disease burden and so it is also not clear if the benefit is the same.
- **Jay Harris** noted that there are patients in whom we only treat the chest wall but there is growing comfort in just treating the chest wall in selected patients at risk, primarily for chest wall recurrence.

consensus

Radiotherapy (RT)

-There is a group not requiring RT as part of BCT.
-Short course RT (e.g. 40 Gy in 15 fractions) be offered as a standart in some patients, and is an option if boost is also planned.
-Following breast conserving surgery partial breast RT may be used only in the absence of adverse tumor pathology.

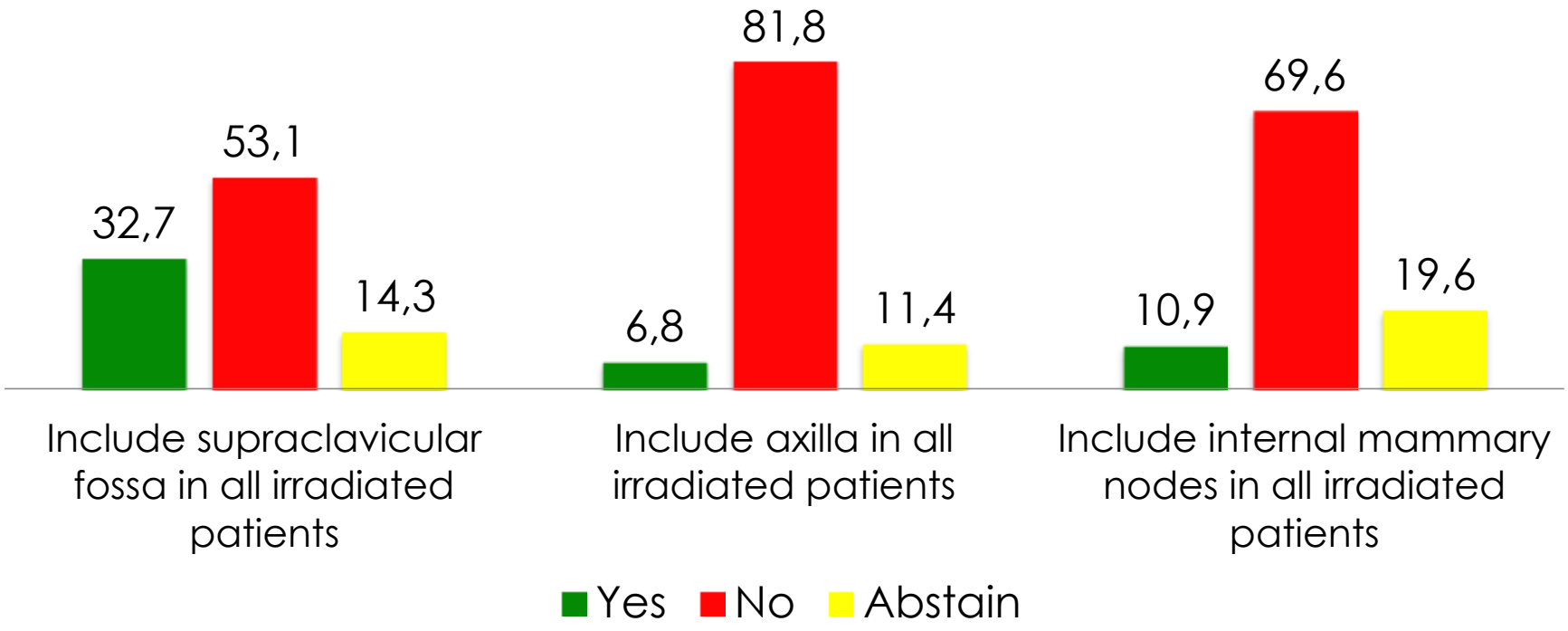
-Postmastectomy RT be standard for patients with,

1. LN > 3 positive.
2. LN 1-3 positive, with adverse pathology
3. LN 1-3 positive in young age (< 40)

Postmastectomy RT should not be standard for patients with adverse pathology (like Her2, grade) regardless of nodes.
Postmastectomy RT should be standard for patients with tm > 5 cm (regardless of nodes) or with positive deep/radial margins.

Radiotherapy (RT)

Nodal areas requiring RT should:



Should nodal areas requiring RT be influenced by response to neoadjuvant therapy?

Not RANDOMİZED DATA

VOLUME 30 · NUMBER 32 · NOVEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Predictors of Locoregional Recurrence After Neoadjuvant Chemotherapy: Results From Combined Analysis of National Surgical Adjuvant Breast and Bowel Project B-18 and B-27

Eleftherios P. Mamounas, Stewart J. Anderson, James J. Dignam, Harry D. Bear, Thomas B. Julian, Charles E. Geyer Jr, Alphonse Taghian, D. Lawrence Wickerham, and Norman Wolmark

See accompanying editorial on page 3913 and article on page 3916

Not RANDOMİZED DATA

Table 1. Rates of Locoregional Recurrence After Mastectomy in NSABP B-18 and B-27

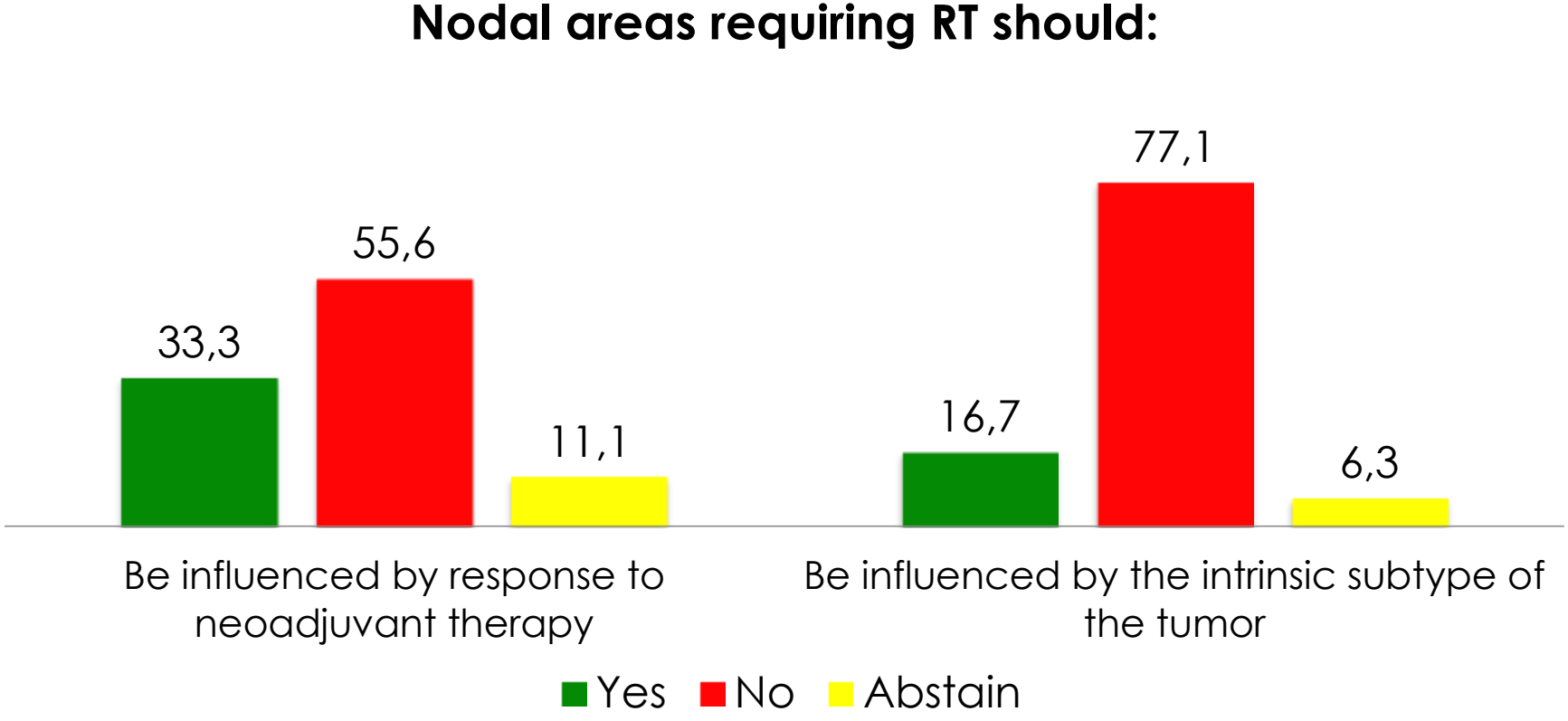
Lymph Node Stage at Presentation	Tumor Size at Presentation (cm)	Residual Invasive Tumor After Preoperative Chemotherapy		No. of Patients in Each Subset	10-Year Cumulative Incidence of LRR (%)
		Breast	Lymph Node		
Clinically node negative	≤ 5	–	–	46	6.5
		+	–	178	6.3
		Any	+	184	11.2
	> 5	–	–	16	6.2
		+	–	95	11.8
		Any	+	179	14.6
Clinically node positive	≤ 5	–	–	21	0.0
		+	–	37	10.8
		Any	+	143	17.0
	> 5	–	–	11	0.0
			–	33	9.2
		Any	+	128	22.5

Abbreviations: LRR, locoregional recurrence; NSABP, National Surgical Adjuvant Breast and Bowel Project.

- **NSABP-RTOG 9353**
  - T1-3 N1 [nodal mets confirmed with FNA]
  - ypN0 found at axillary disseciton after neoadjuvant chemo.
    - Post BCS → Breast RT **vs**. Breast + regional RT
    - Post MRM → observ. **vs.** PMRT

- **A011202 (ACOSOG + CALGB+NCCTG)**
  - T1-3 N1
  - ypN+ found at SLNB after neoadjuvant chemo.
    - All pts will get breast/Chest wall + none dissected supra- level 3 RT.
      → Axillary dissection **vs.** axillary RT

Radiotherapy



Comments

- **Sibylle Loibl** added that nodal radiotherapy should not be influenced by the response to neoadjuvant therapy. We do not have much data in this area and perhaps we need to reflect that in a patient with pCR maybe the nodes do not need to be irradiated. Another panelist added that we have recent clinical trial data addressing this point.
- **Partridge** commented that young age, given the uncertainty over whether this will remain a prognostic and predictive factor, is one factor we take into account when thinking about the need for post-mastectomy irradiation and because they have the highest risk of locoregional recurrence.

Comments

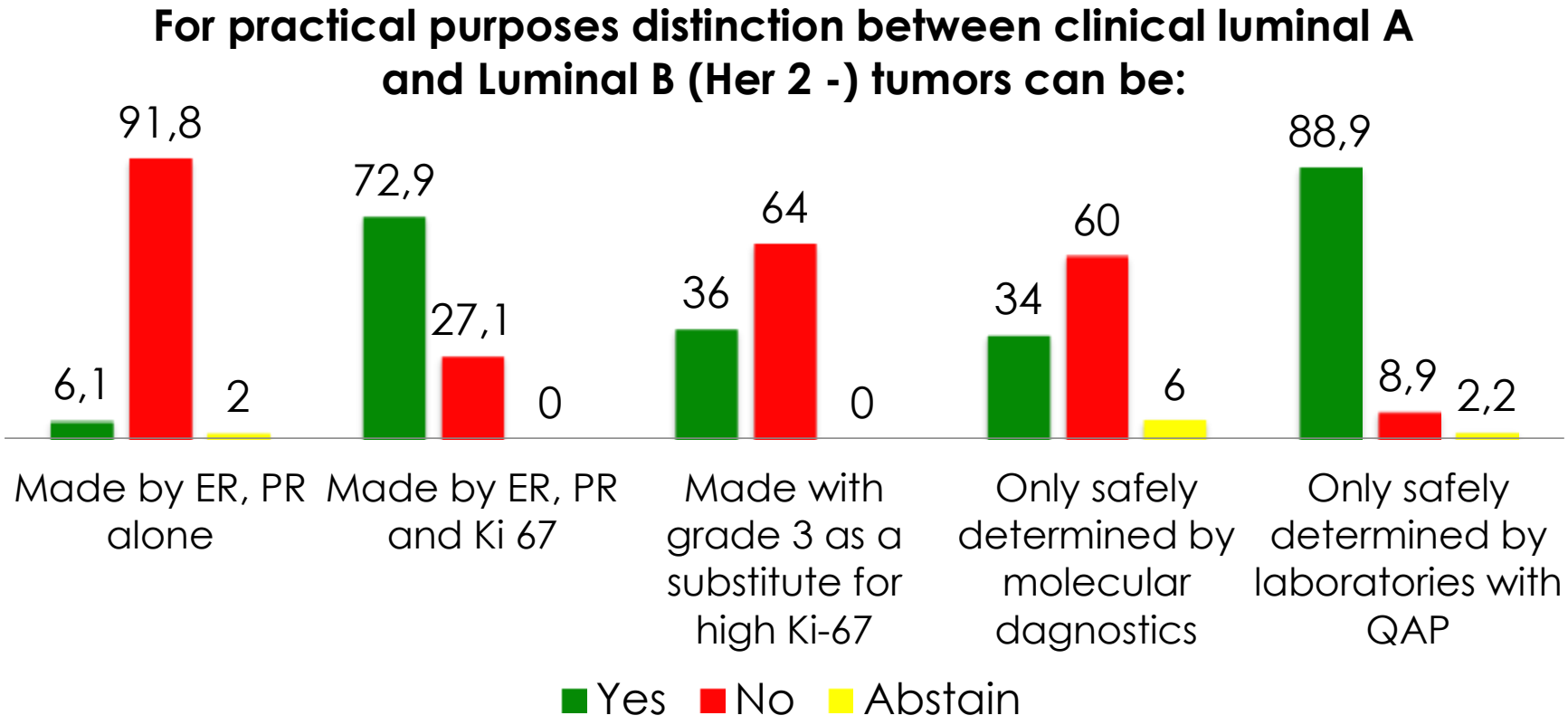
Alan Coates added that, as we move on to pathology in this process, we have seen that the local therapists are not too keen on changing their treatment based on pathology. But that is not the case when we come to think about systemic therapy. The real areas where we need to progress this time are in the areas of luminal disease that is HER-2 negative and there we have a great deal to look at. We now have ample evidence that you can look for prognostic factors and most of the tests you can look at will give you prognostic information. More important is the predictive scale, what he refers to as the chemofutility axis - are there patients, even though they may be at risk, for whom chemotherapy simply does not work. That's a very different question, it is a predictive question and the evidence for this is strong. If chemotherapy adds nothing then we are going to need labels within this space of luminal HER-2 negative disease. He would prefer to keep something that refers to the underlying types and we need to keep in mind that the ultimate reason for exploring this space is to give or withhold toxic chemotherapy.

Eric Winer added that surgeons and radiation oncologists are right to consider biology to help them change their treatments but they just don't know how to do it yet. We are seeing the struggle to incorporate biology in the decision making process

Conference Topic

Pathology

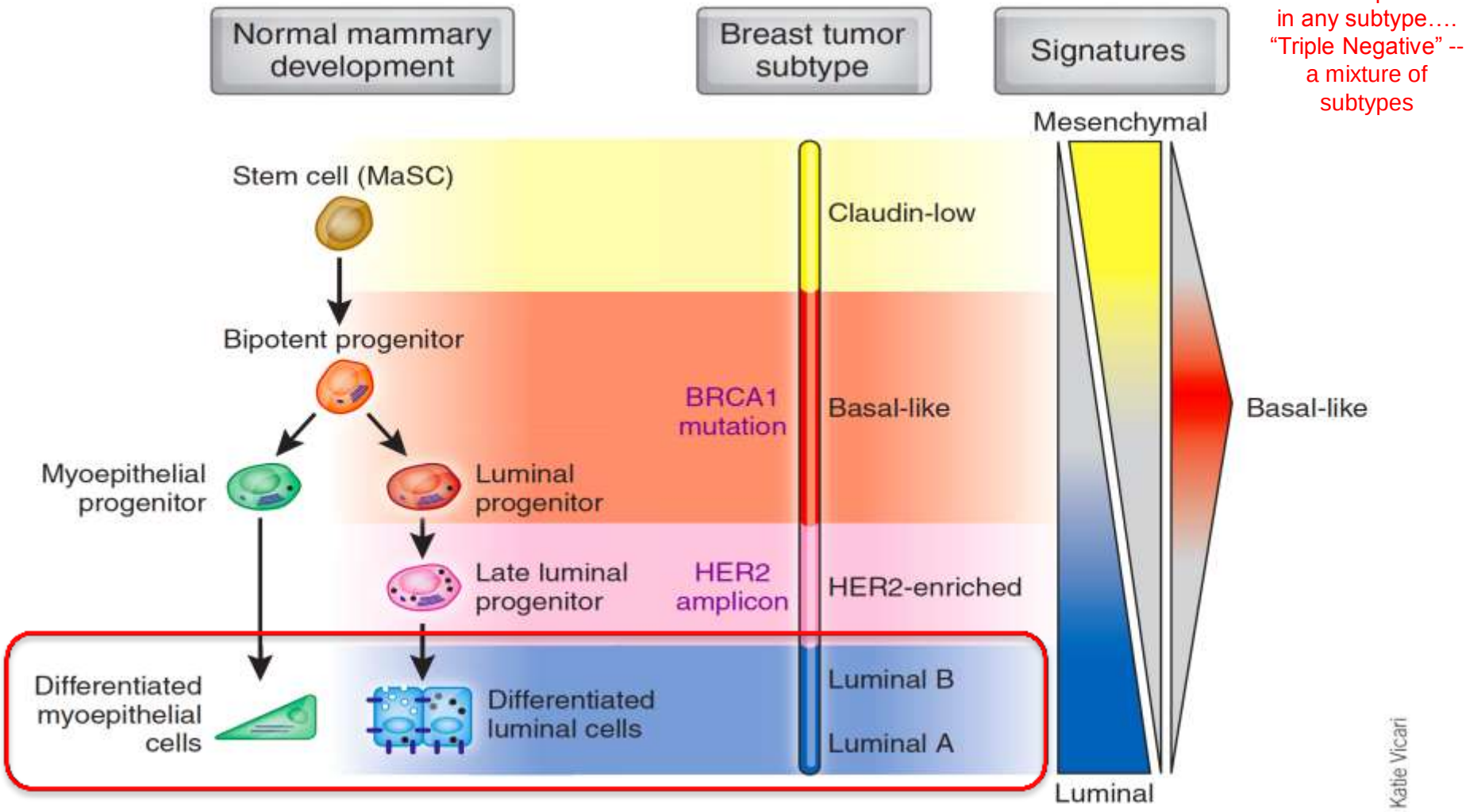
Pathology



QAP - quality assurance program

Breast Cancer Subtypes

HER2 and ER can be expressed in any subtype…. "Triple Negative" -- a mixture of subtypes



Pratt and Perou, Nature Med 15:842, 2009

St. Gallen 2011: "Shorthand" Determination of Breast Cancer Subtypes

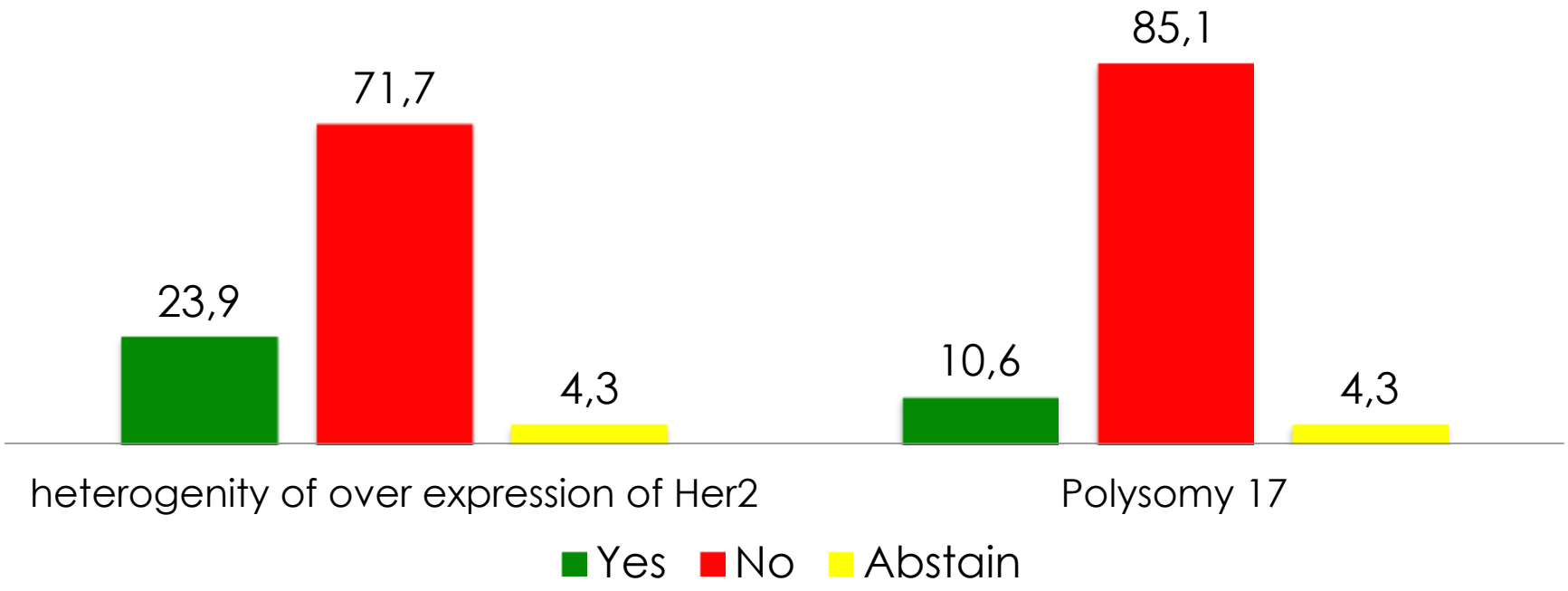
Intrinsic Subtype	Surrogate Definition
Luminal A	ER and/or PgR(+), HER2(-) Ki-67 low (<14%)*
Luminal B1	ER and/or PgR(+), HER2(-) Ki-67 high
Luminal B2	ER and/or PgR(+), HER2(+) Any Ki-67
HER2 over-expression	ER and PgR absent, HER2(+)
Basal-like	Triple negative ductal (not medullary, adenoid cystic)

* Using PAM5O cutpoint from Cheang et al. JNCI 2009

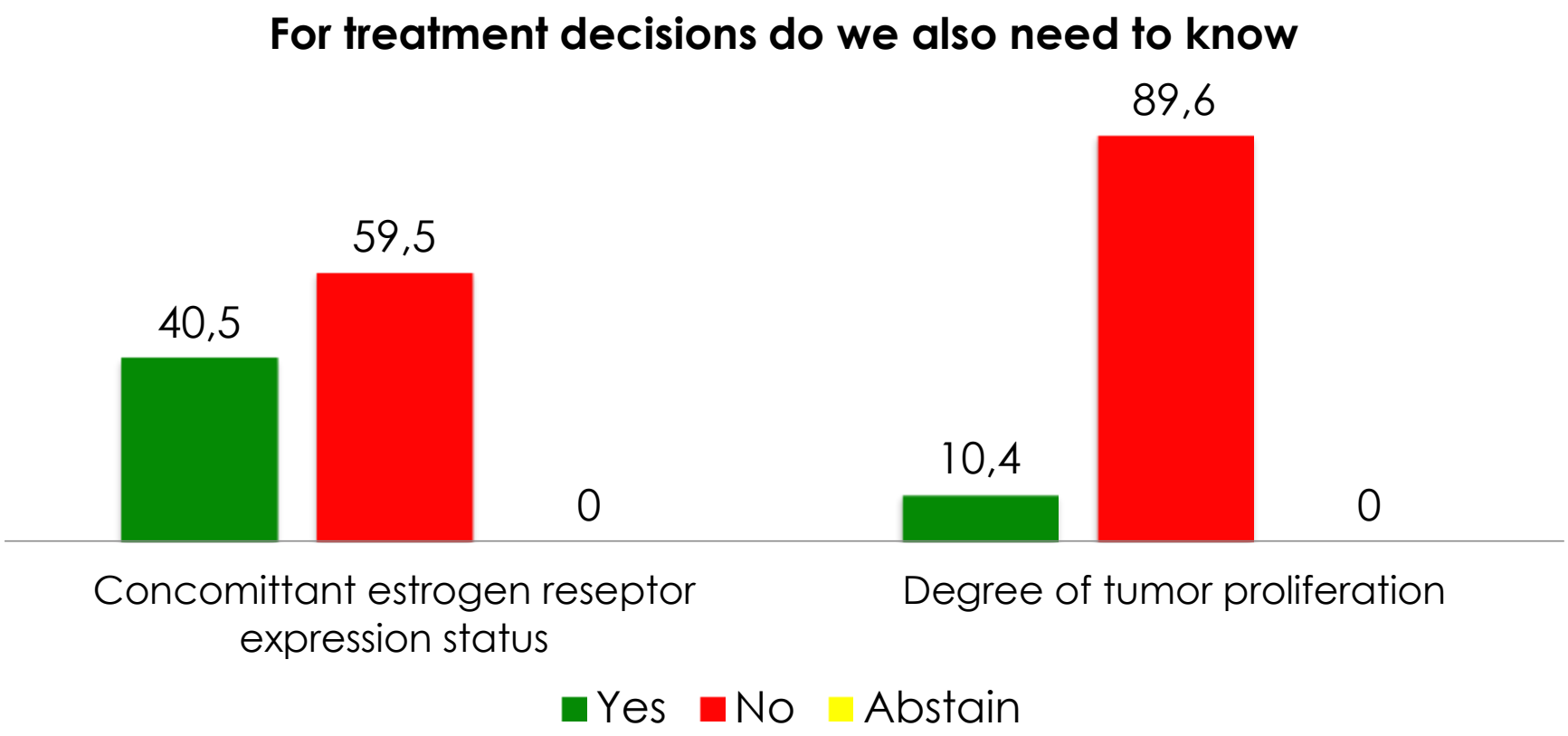
Goldhirsch A. Annals Oncol 2011, doi:10.1093/annonc/mdr304

Pathology: HER2

In the determination of Her2 status for anti Her2 treatment purposes, do we need to know:

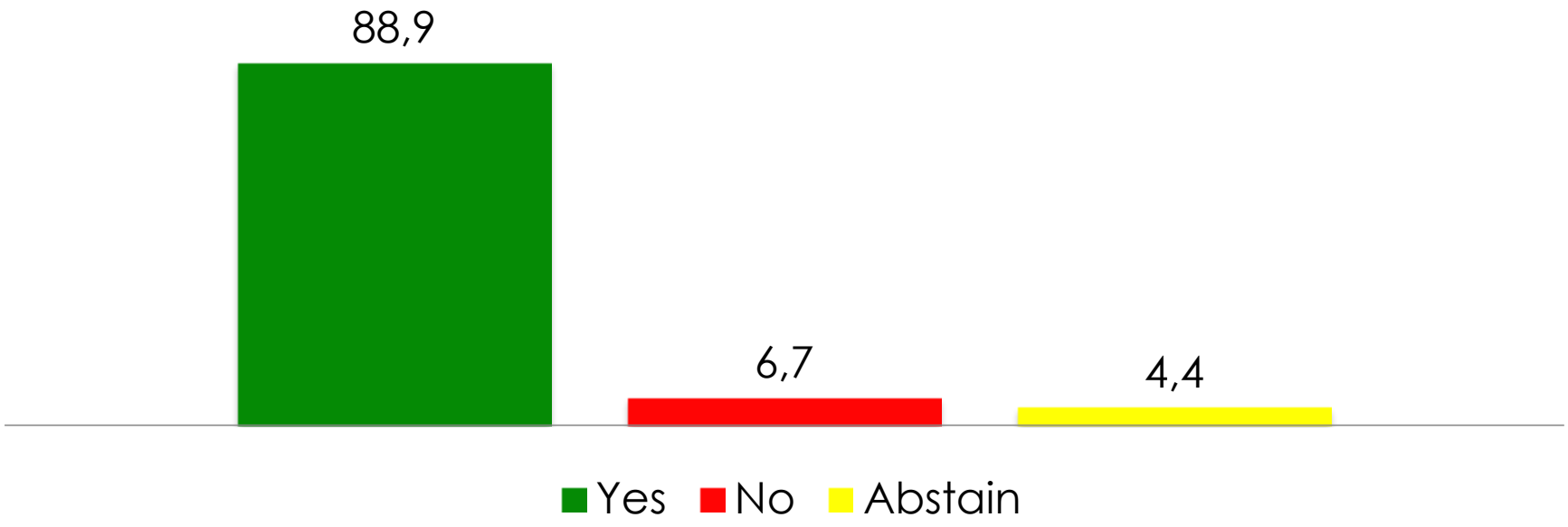


Pathology: HER2

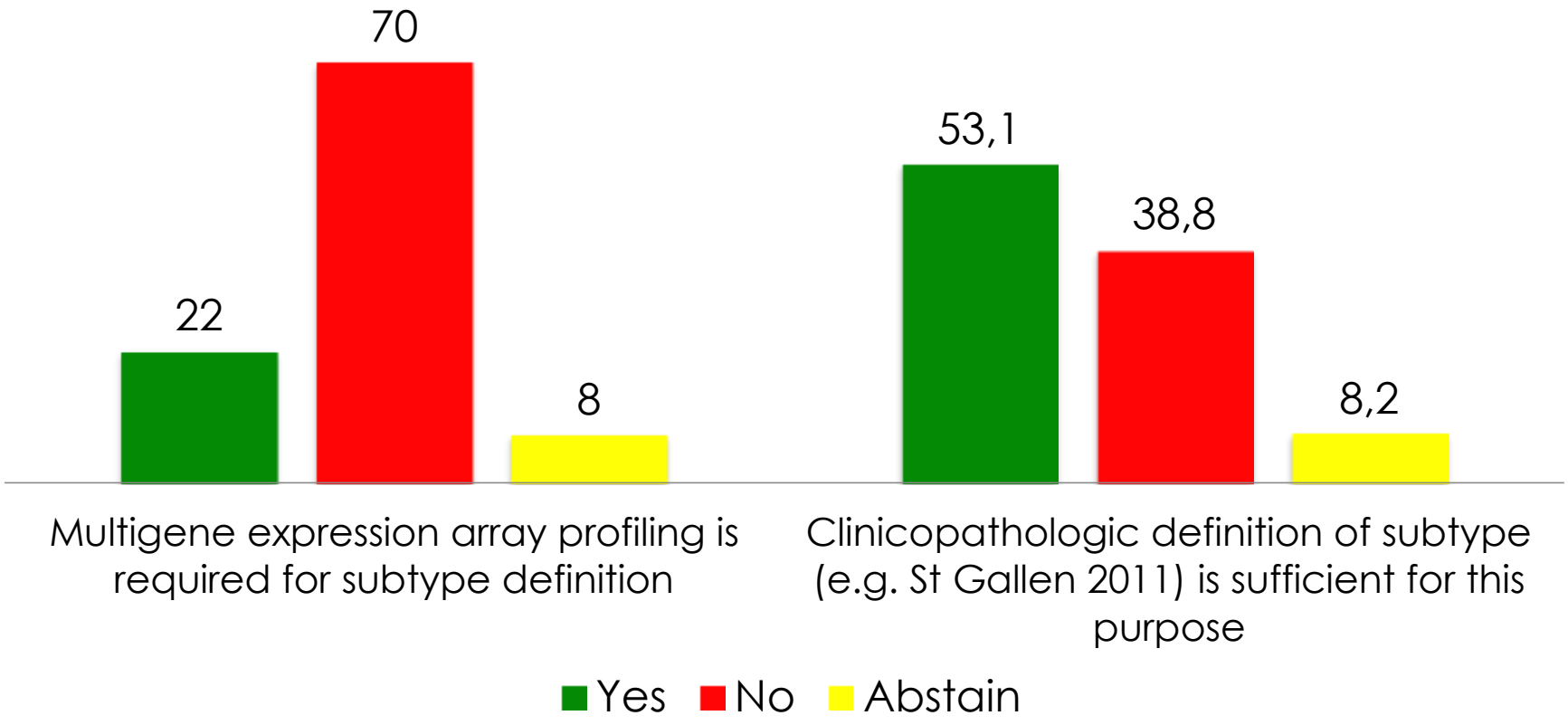


Pathology: Subtypes

Does intrinsic subtype may influence whether or not chemotherapy is used in the adjuvant regimen?

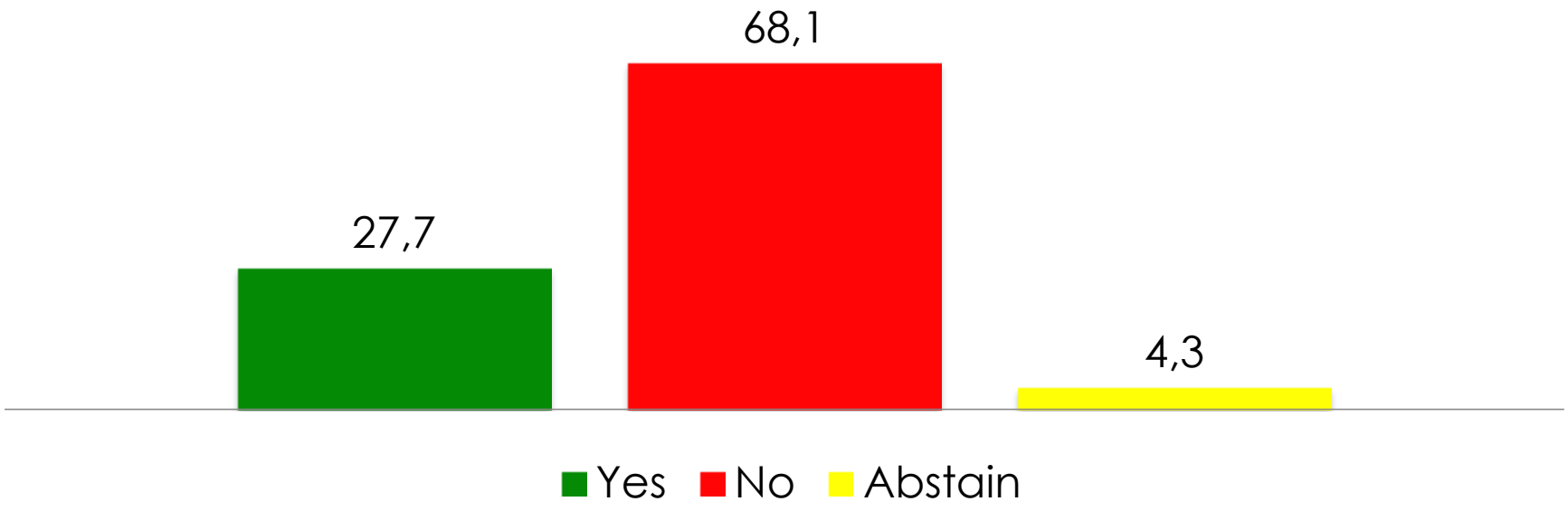


Pathology: Subtypes

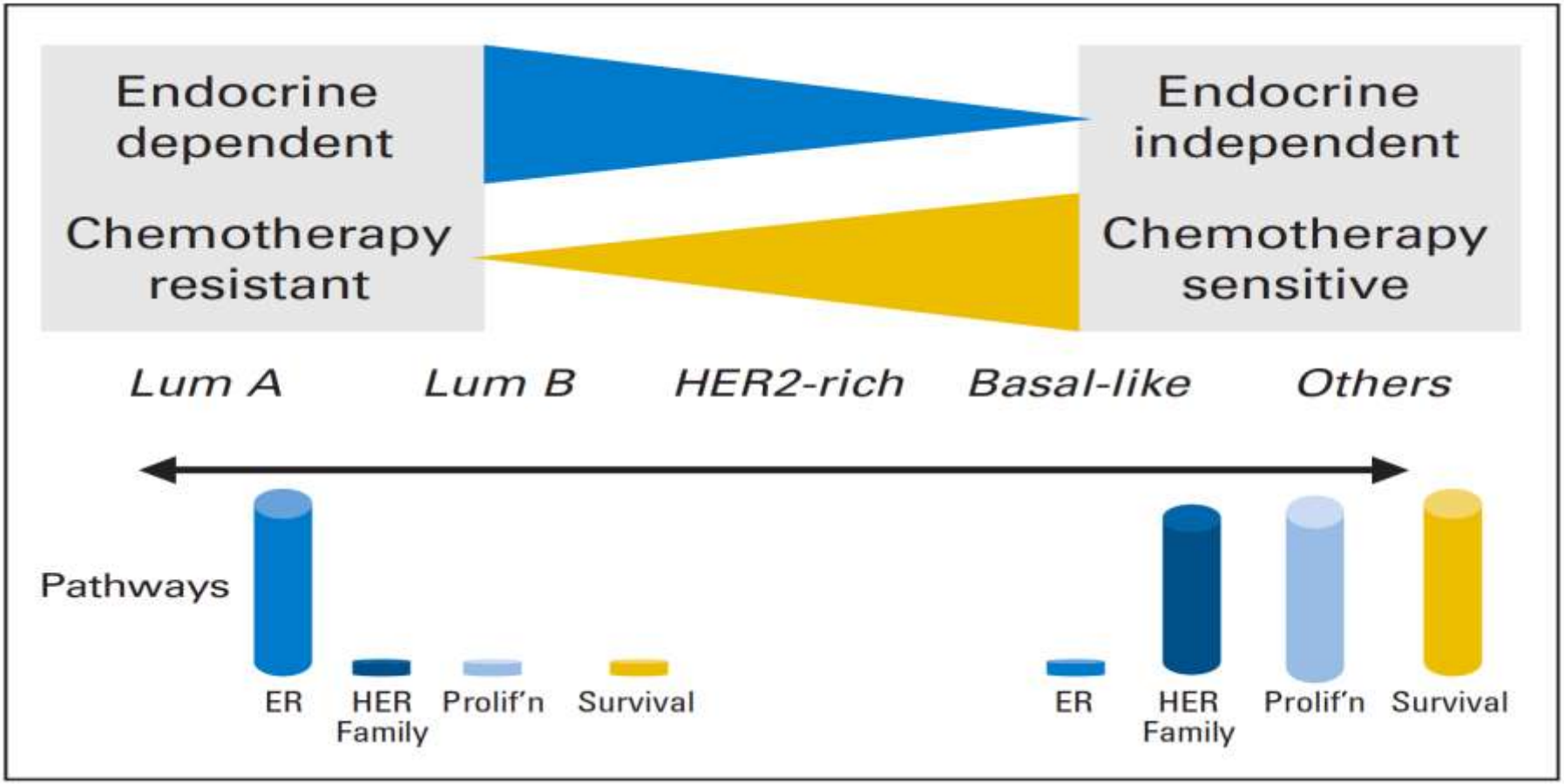


Pathology: Subtypes

Choice of cytotoxic chemotherapy regimen should be influenced by intrinsic subtype ? (whether you get anthracycline vs no etc)



A Theoretical Spectrum of Sensitivity to Adjuvant Systemic Therapy by Intrinsic Subtypes



Hayes DF. Journal of Clinical Oncology, 30(12):1264-1267, 2012

Systemic treatment recommendations

'Subtype'	Type of therapy	Notes
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status).
'Luminal B (HER2 negative)'	Cytotoxics ± endocrine therapy	Inclusion and type of cytotoxics may depend on level of endocrine expression, perceived risk and patient preference.
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2+ endocrine therapy	No data are available to support the omissionof cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk may be observed without treatment
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine non responsive	Cytotoxics	Medullary and apocrine carcinomas may not require any adjuvant cytotoxics (if node negative).

Goldhirsch A. Annals Oncol 2011, doi:10.1093/annonc/mdr304

The Recurrence Score® Results Uses Key Genes Linked to Critical Molecular Pathways

16 Breast Cancer related genes

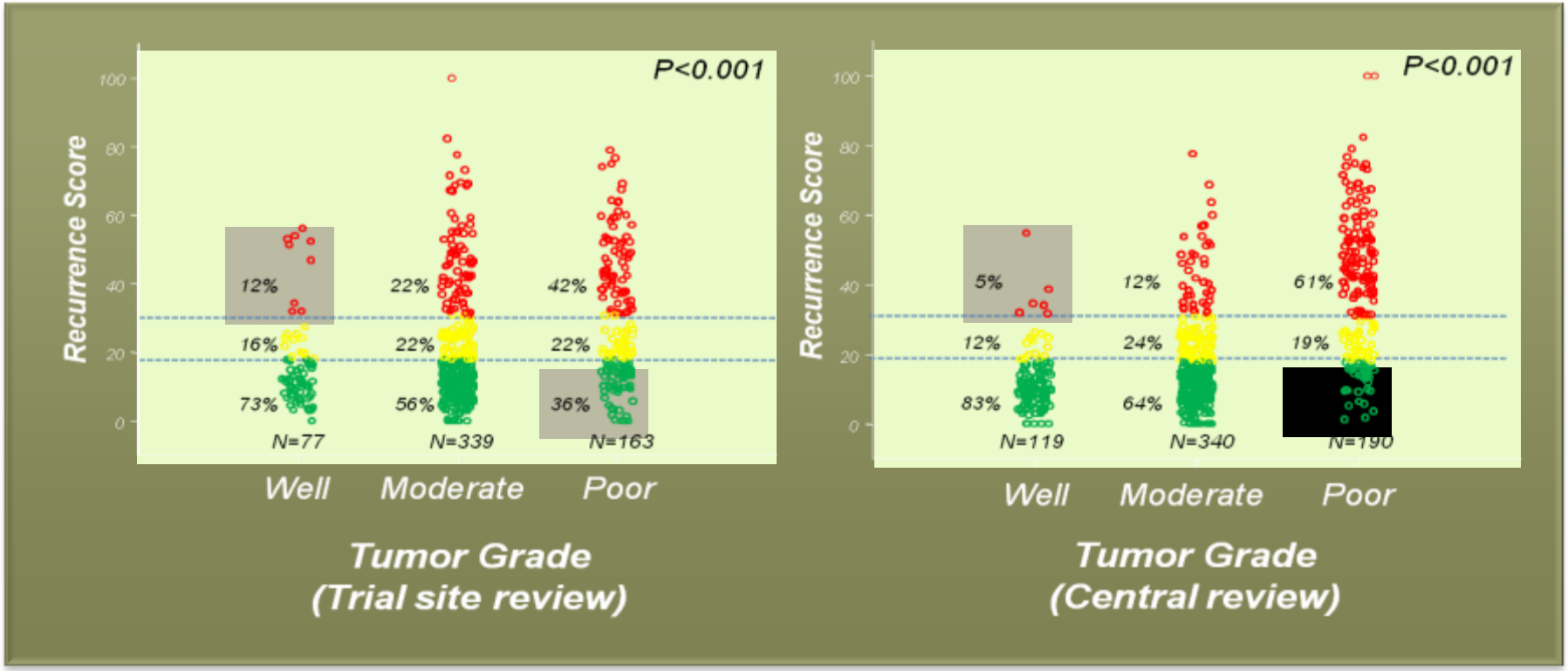
Estrogen	Proliferation	HER2	Invasion	Others
ER PR Bcl2 SCUBE2	Ki-67 STK15 Survivin Cyclin B1 MYBL2	GRB7 HER2	Stromelysin 3 Cathepsin L2	CD68 GSTM1 BAG1

5 Reference genes

Beta-actin | GAPDH | RPLPO | GUS | TFRC

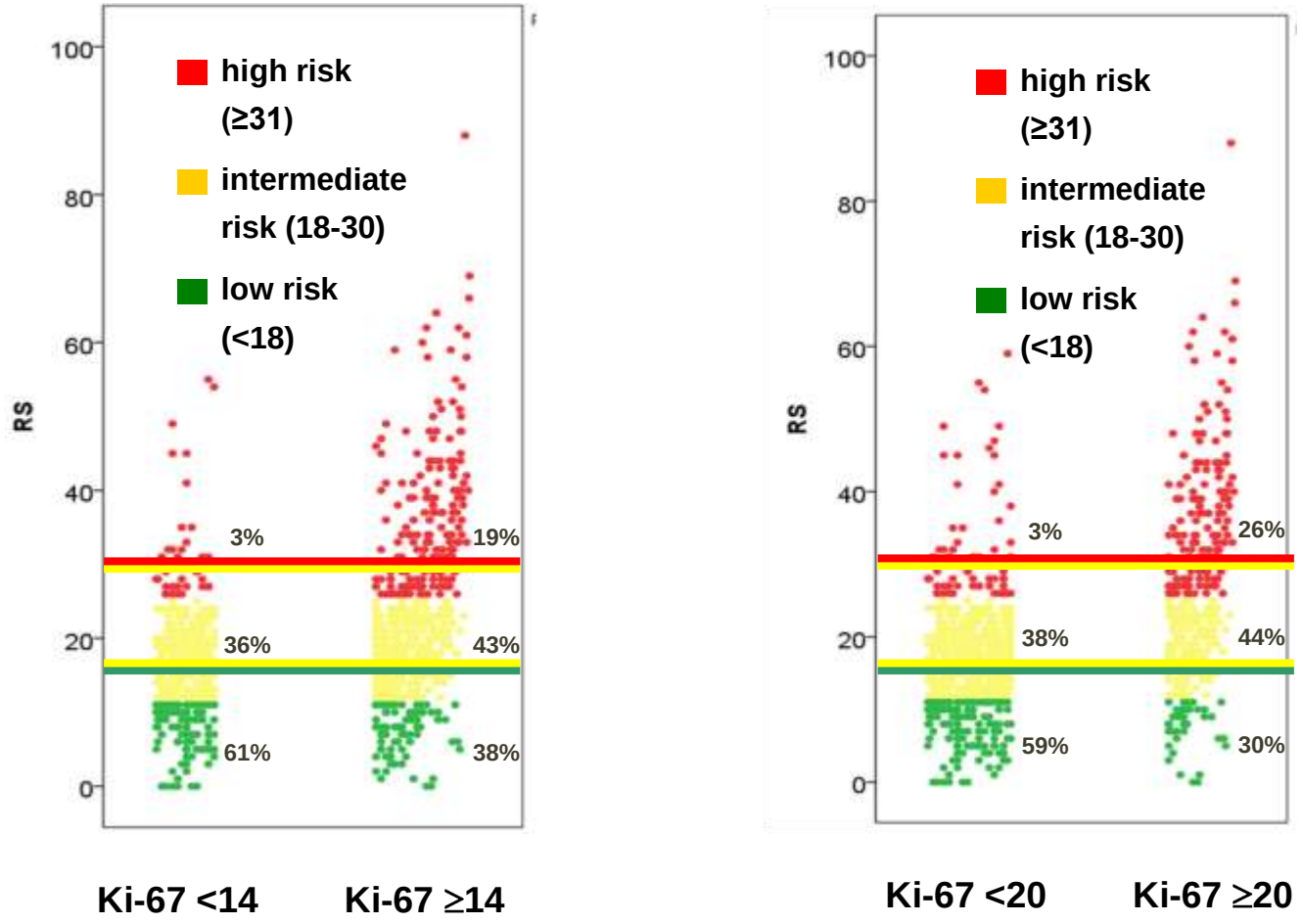
Paik S, et al. *N Engl J Med.* 2004;351:2817-2826.

NSABP B-20: Significant proportion of high-grade tumors have a low Recurrence Score® result and many low-grade tumors have a high result



Paik S, et al. *J Clin Oncol*. 2006;24:3726-3734.

Recurrence Score® by Ki-67 Standard Cut-offs

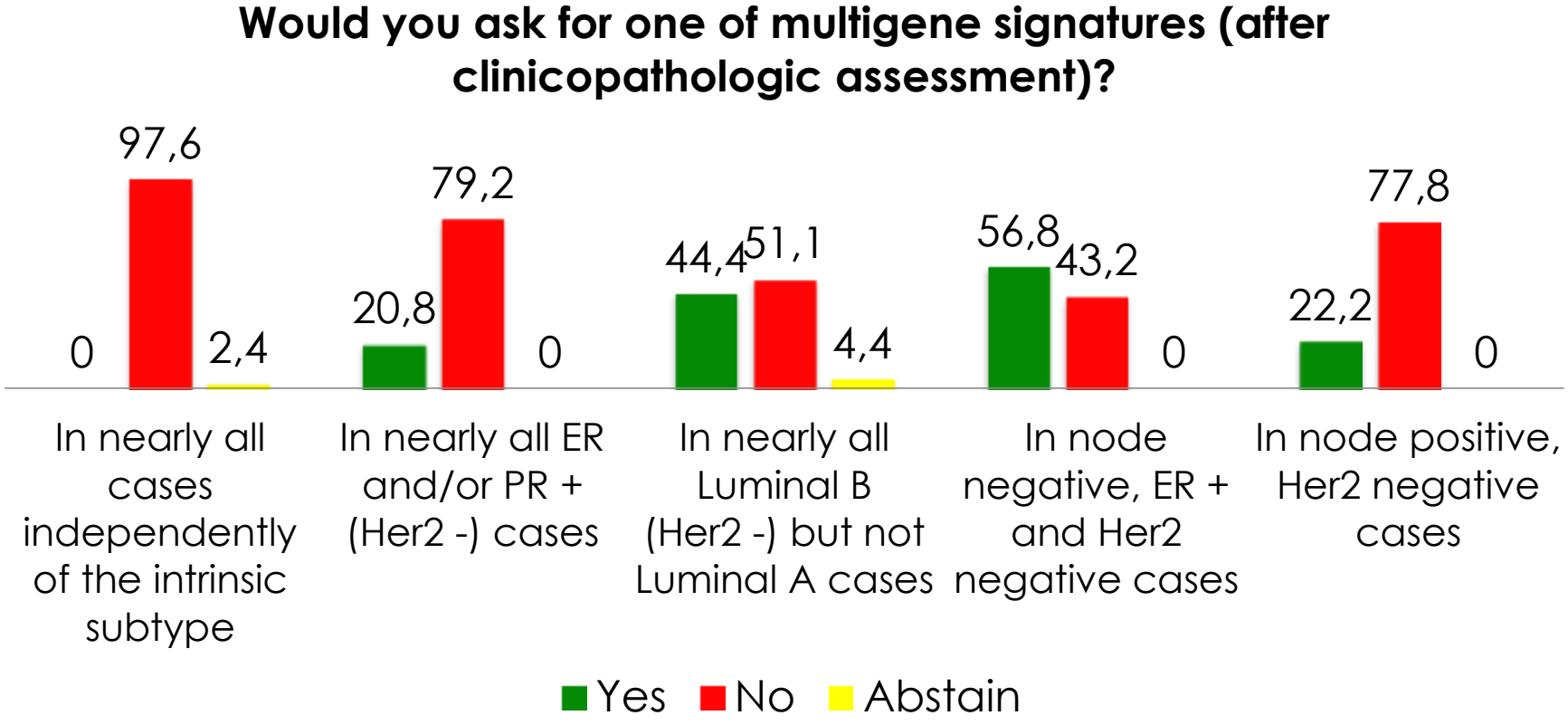


Gluz O et al, *San Antonio Breast Cancer Symposium®* 2011; Abstract S4-3..

Oncotype DX® Is the Only Multigene Expression Assay Incorporated into NCCN®, ASCO®, and St. Gallen's Guidelines

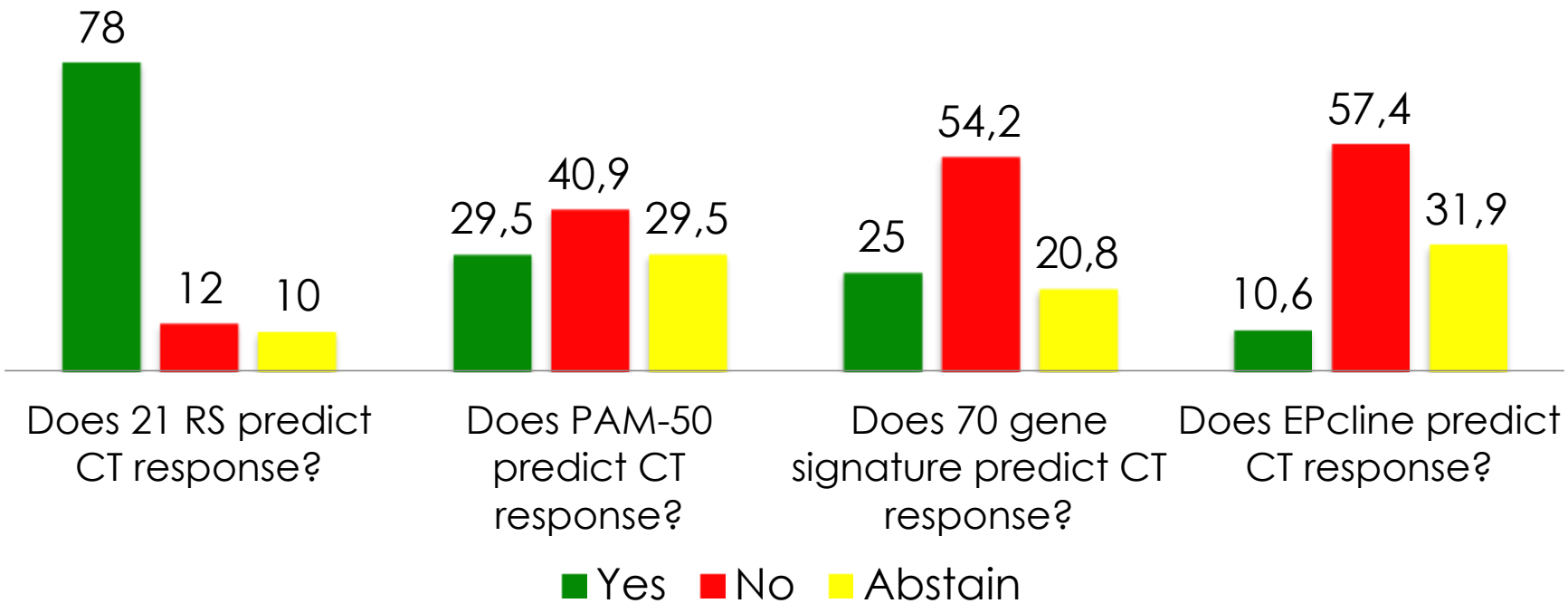
NCCN GuidelinesTM	Consider use in > 0.5 cm, HR+, HER2– disease pT1, pT2, or pT3 and pN1mi (≤ 2 mm axillary node metastasis)
ASCO Guidelines	Newly diagnosed patients with node-negative, ER+ breast cancer who will receive tamoxifen
St. Gallen 2011 Consensus	Oncotype DX has been shown to predict chemotherapy benefit among patients with HR+ disease

Multi-Gene Signatures



Multi-Gene Signatures

In an endocrine responsive* cohort:



*i.e. Any expression of ER and/or PR

Comments

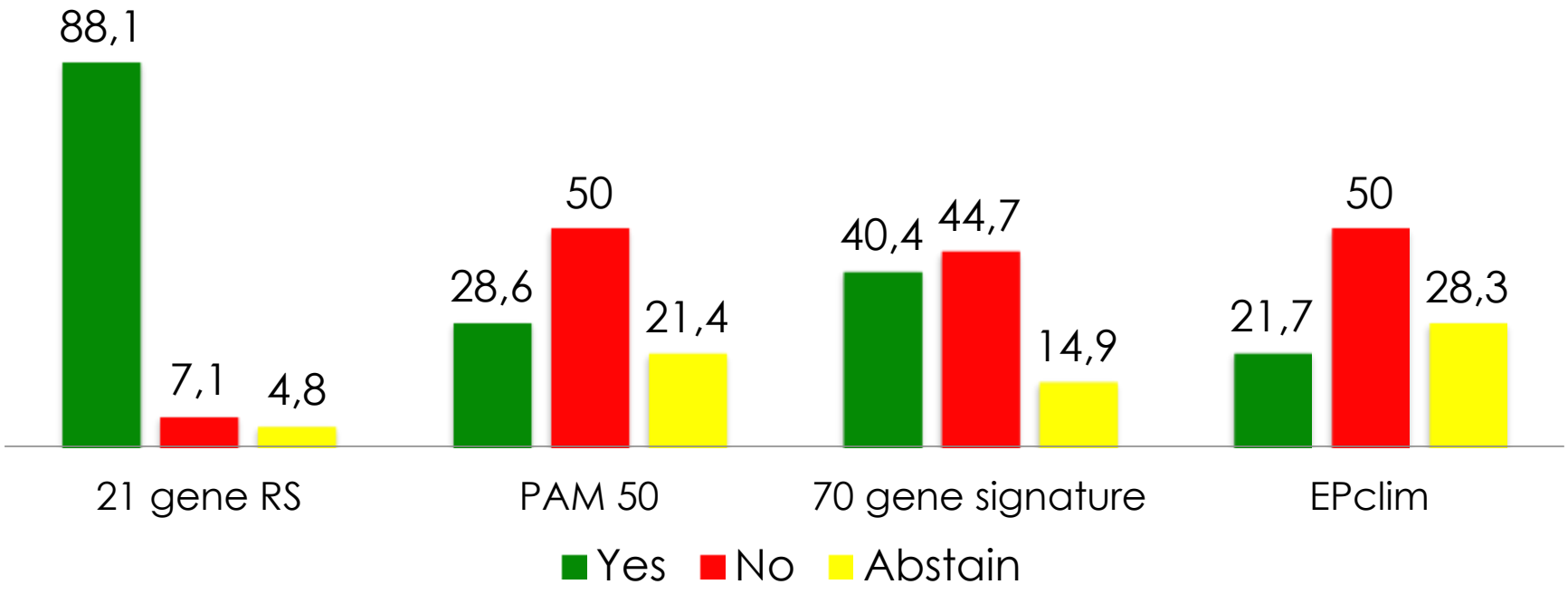
- **Jay Harris** stated that regarding the actual assays, there remains a lot of variability for example it would be a tremendous mistake for this panel to recommend that Ki67 done by IHC should be used to determine whether or not chemotherapy should or should not be given
- **Martine Piccart** also added that the Ki67 is an unreliable assay we should not make recommendations for women based on this assay that has no demonstration of analytical validity. Perhaps a compromise is in grade III tumour where you can be relatively confident in Ki67 but for all the other tumours Ki67 is not the right way to go right now.

Comments

- Pathologist **Frederique Penault-Llorca's** perspective is that we should try to have agreement on the percentage through quality assurance procedures. Overall, we can manage to do Ki67 even though it is imperfect (particularly in the range 20-30%). We are not very good with grade II tumours, that's a fact, but we do actually have good reproducibility for grade III tumours (i.e. those with high Ki67 expression).
- **Eric Winer** concluded that it is important to look at the pathology report with a healthy dose of skepticism - particular the results of any single test. We will be a place in a few years to offer much more precise diagnostics. We are now training molecular pathology and we are far beyond the morphological diagnosis.

Multi-Gene Signatures

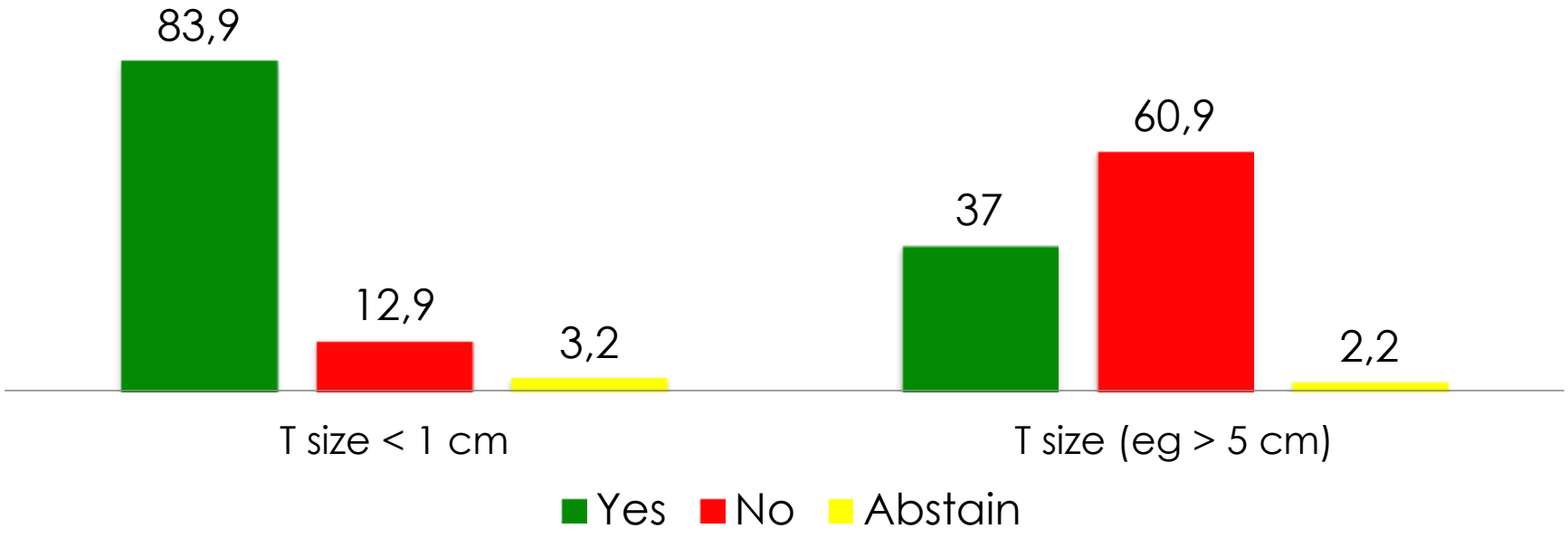
In an endocrine responsive* cohort, selection of patients who might forego chemotherapy can be partially based on:



*i.e. Any expression of ER and/or PR

Molecular Diagnostics

In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because



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Molecular Diagnostics

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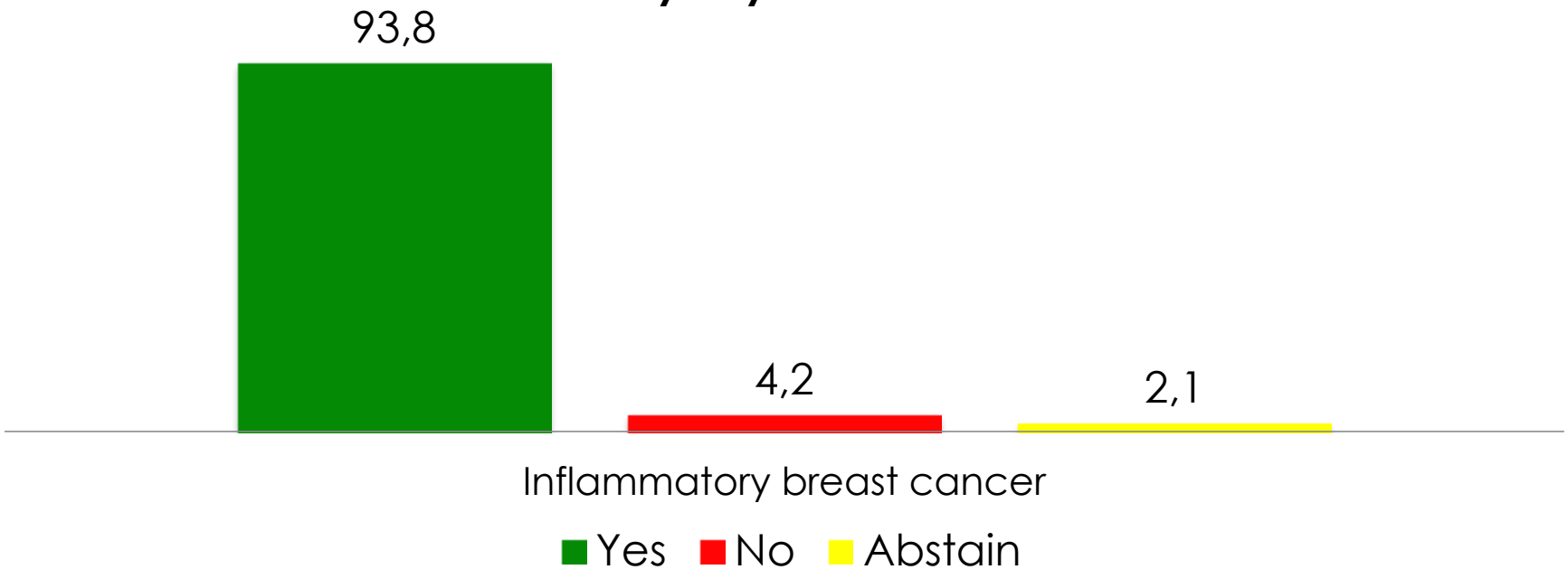
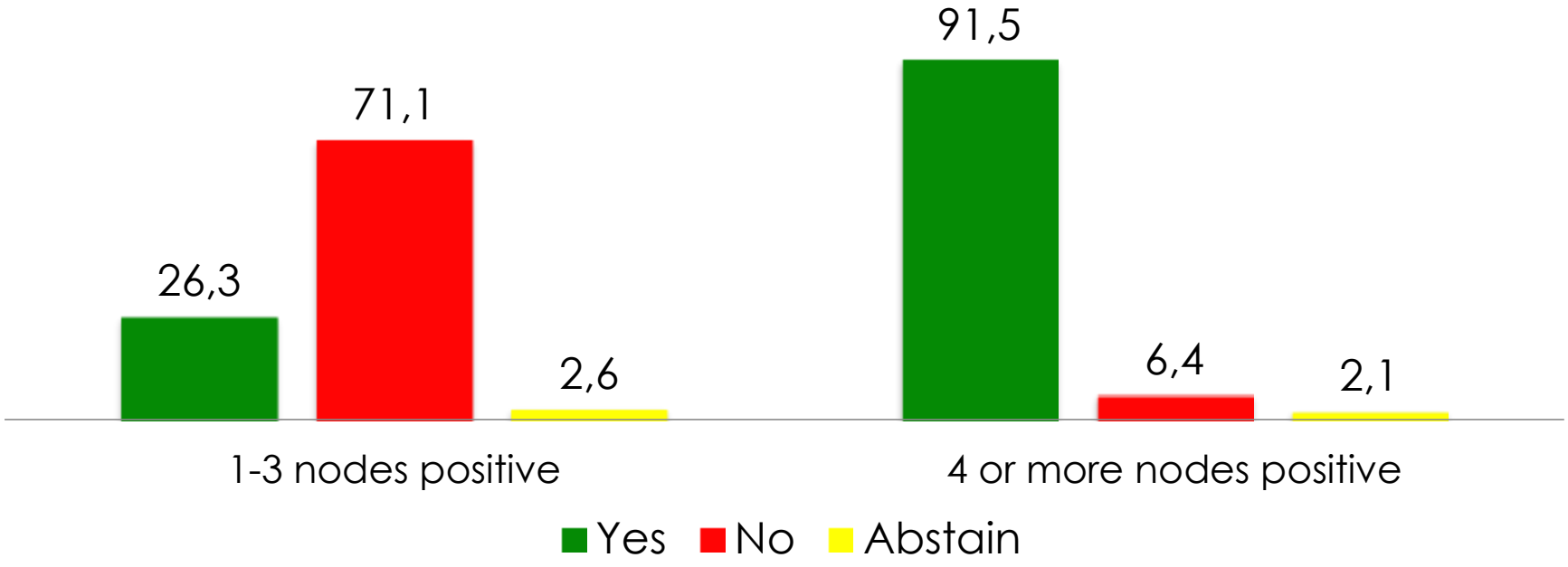


*i.e. Any expression of ER and/or PR

Molecular Diagnostics

In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because



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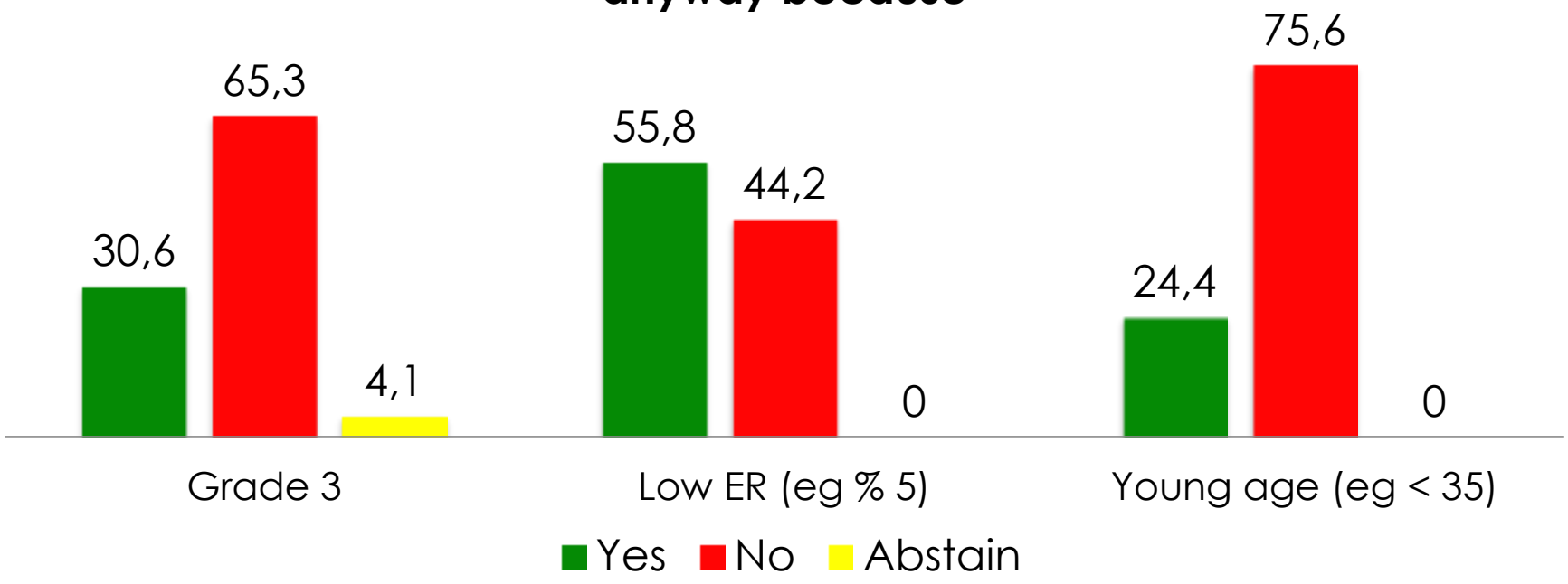
Molecular Diagnostics

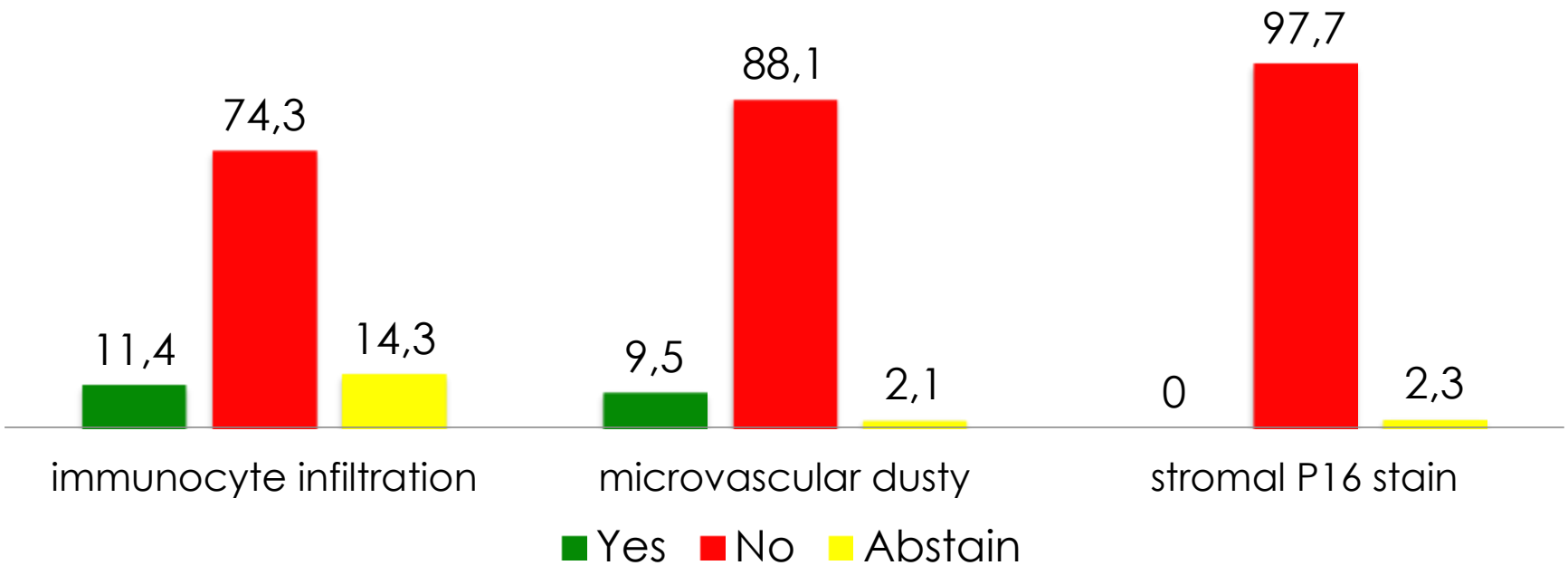
In an endocrine responsive* cohort, molecular diagnostics can be omitted if chemotherapy would not be given anyway because



*i.e. Any expression of ER and/or PR

Stroma

Pathologic features of the stroma which should influence therapy choice in routine clinical practice include:



consensus

PATHOLOGY 1

- For practical purposes distinction between luminal A and Luminal B (Her 2 -) tumors can be made by ER, PR, Ki67, and only determined by laboratories with quality assurance program.
- In the determination of Her2 status for anti Her2 treatment purposes, we do not need to know heterogenity of over expression of Her2.
- In Her2 positive patients estrogen receptor status, and degree of tumor proliferation do not change treatment decisions.

consensus

PATHOLOGY 2

- Intrinsic subtype may influence whether or not chemotherapy is used in the adjuvant regimen.
- Multigene expression array profiling is not required for subtype definition. Clinicopathologic definition of subtype (e.g. St Gallen 2011) is sufficient for this purpose.
- Choice of cytotoxic chemotherapy regimen should not be influenced by intrinsic subtype.

consensus

PATHOLOGY 3

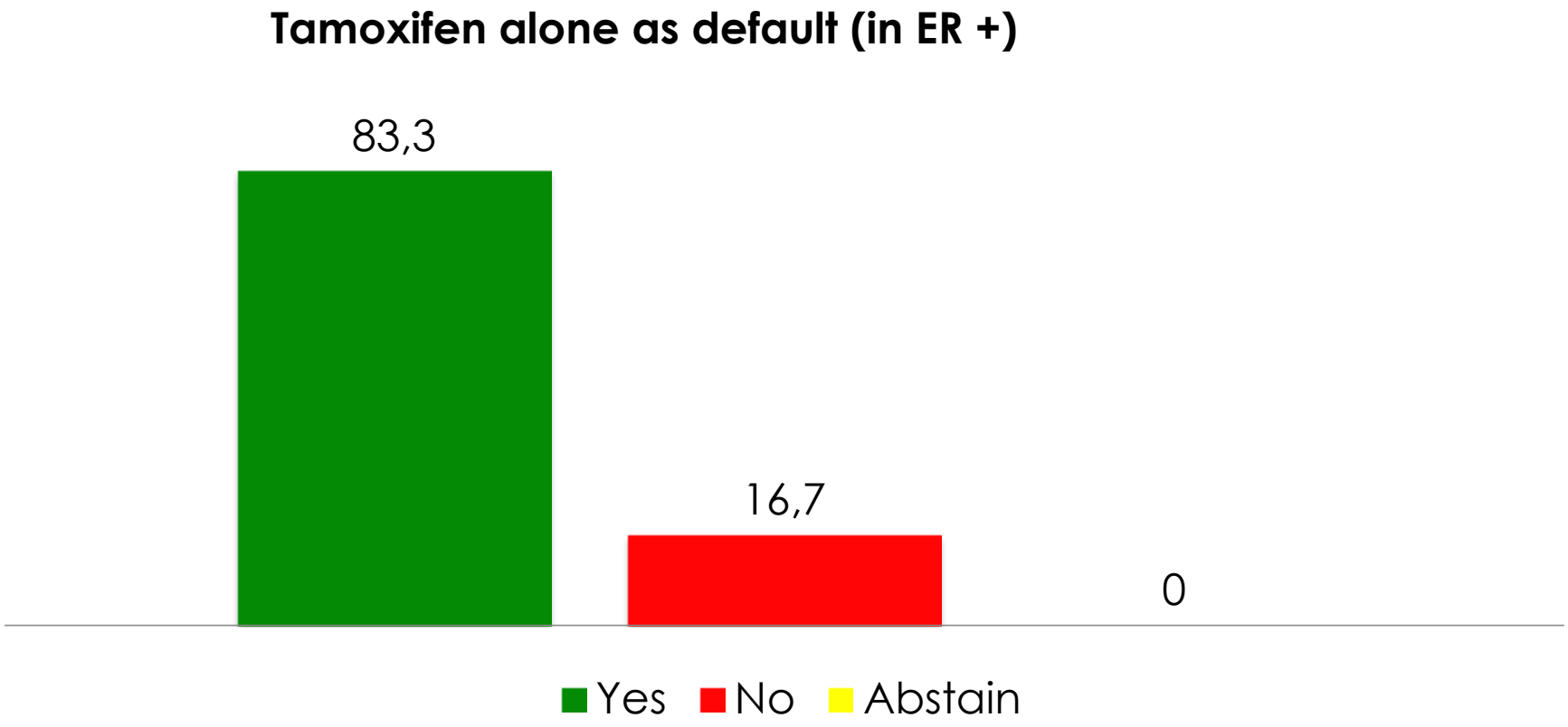
- We would ask for one of multigene signatures (after clinicopathologic assessment) in node negative, ER + and Her2 – cases.
- In an endocrine responsive cohort, 21 gene RS (OncotypeDx) predicts chemotherapy response and selection of patients who might forego chemotherapy can be partially based on this result.
- In an endocrine responsive cohort, if 'tm < 1cm and node negative', inflammatory breast cancer, 4 or more + LN, low ER (e.g. %5)molecular diagnostics can be omitted.

Conference Topic

Endocrine therapy

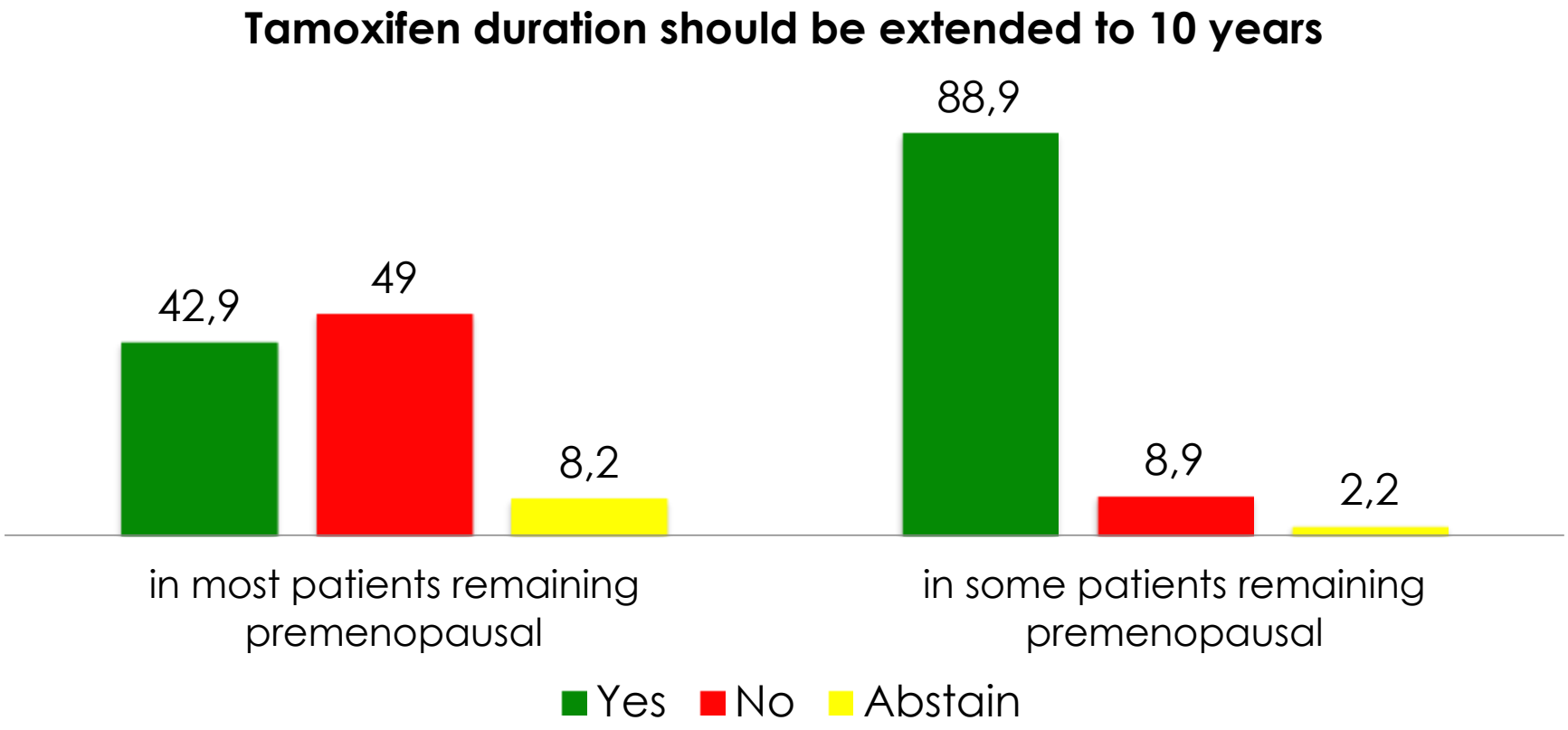
Endocrine Therapies

Establishing Standards for Premenopausal



Endocrine Therapies

Establishing Standards for Premenopausal



Extended Tamoxifen 5 vs 10 Years - ATLAS

Factor	No of ER-Positive Patients (%)
Age < 45 yr	1270 (19%)
Age 45-54 yr	2189 (32%)
Premenopausal	630 (10%)

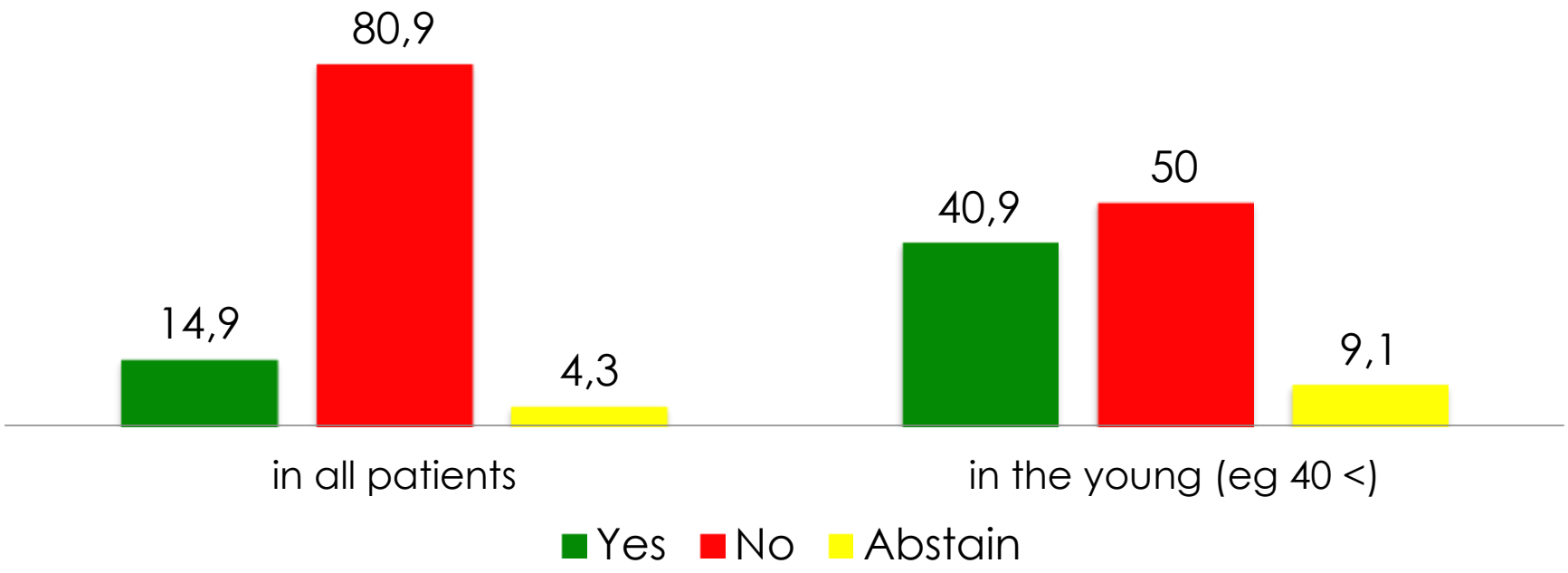
Factor	Ratio of Annual Event Rates (SE)
Age < 55 yr	0.83 (0.07)
Age ≥ 55yr	0.86 (0.07)
Premenopausal	0.81 (0.15)
Post/unknown	0.85 (0.05)

Davies et al, 2013

Endocrine Therapies

Establishing Standards for Premenopausal

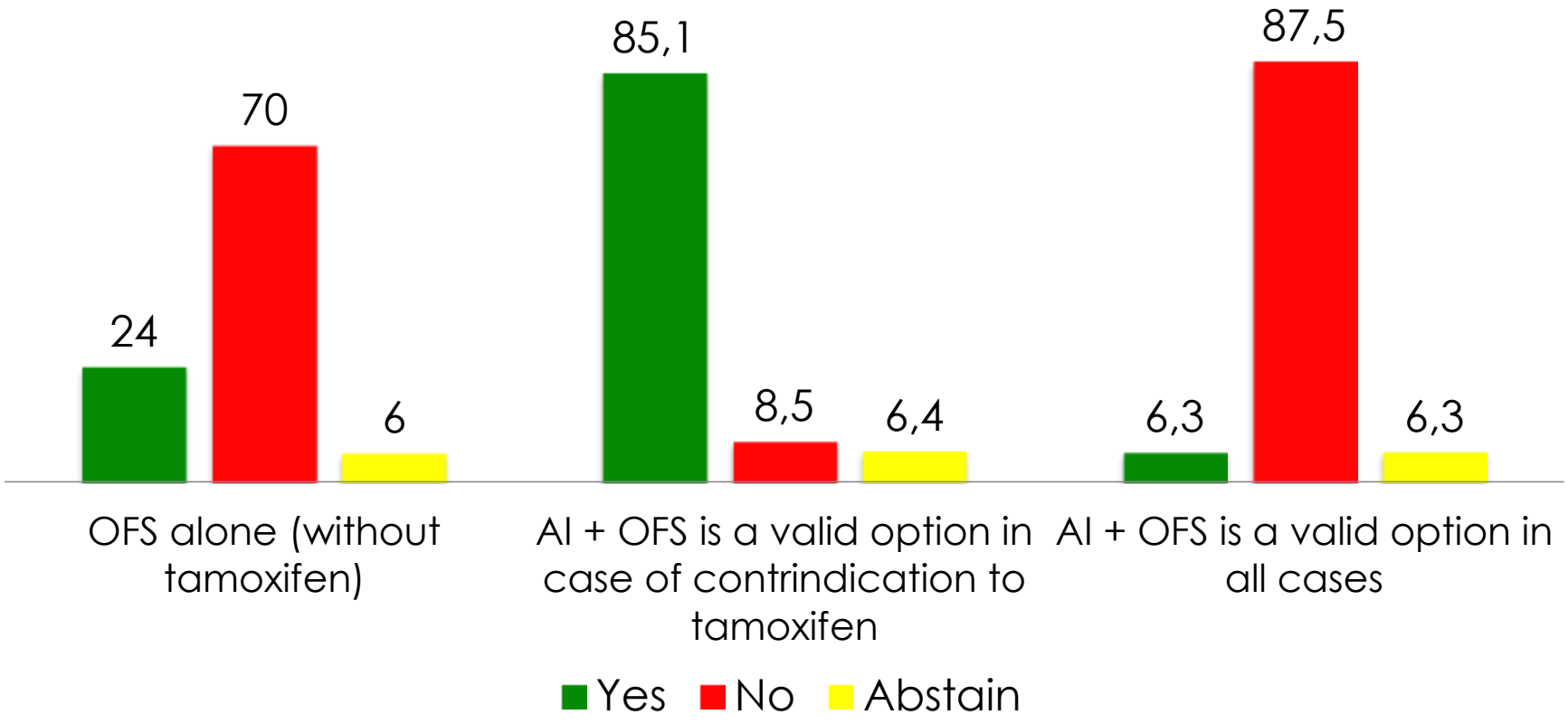
Ovarian function supression (OFS) should be added to tamoxifen



OFS - Ovarian function supression

Endocrine Therapies

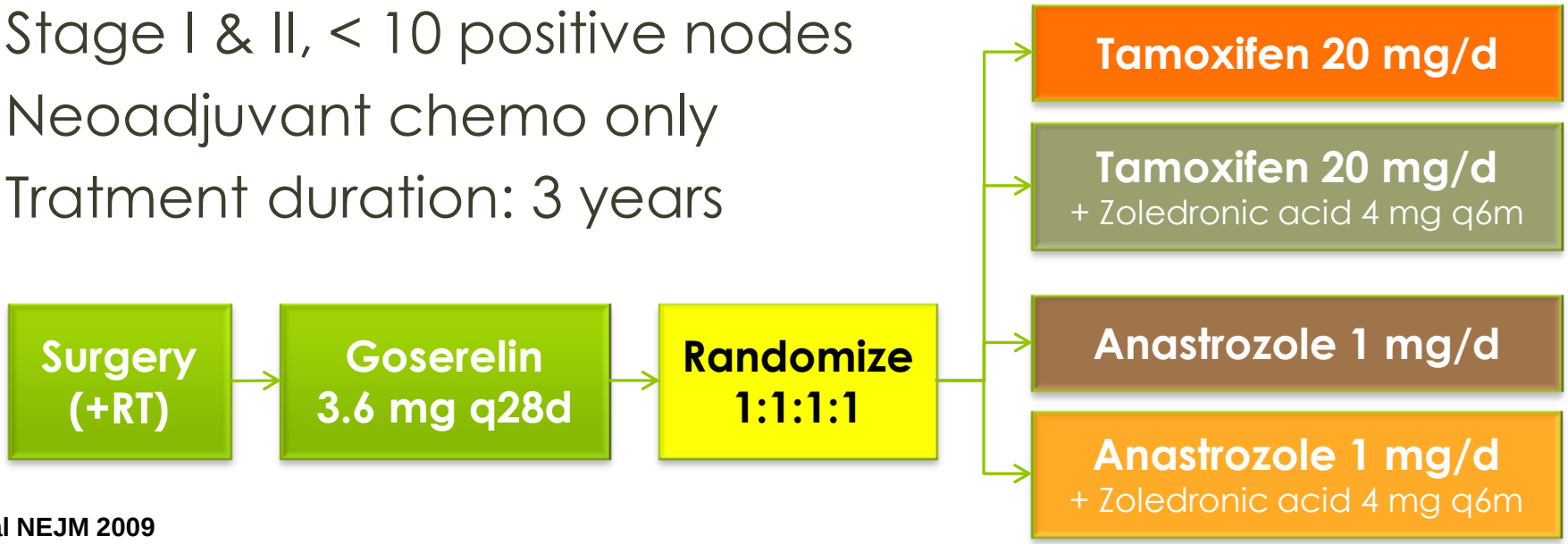
Establishing Standards for Premenopausal



OFS - Ovarian function supression

Optimal Endocrine Therapy For Premenopausal Women ABCSG12

- Accrual 1999-2006
- 1803 premenopausal breast cancer patients
- Endocrine – responsive (ER and / or PR positive)
- Stage I & II, < 10 positive nodes
- Neoadjuvant chemo only
- Tratment duration: 3 years



Gnant et al NEJM 2009

Worse OS but not RFS with AI in ABCSG12 at 62 Months Median Follow-up

DFS	1.08 (0.81-1.44) p=0.591
Overall survival	**1.75 (1.08-2.83) p=0.02**

- Why?
- 96% of women enrolled are alive
- No clear explanation
- No obvious differences in cause of death
- Chance? Methods? Inadequate salvage?
- Role of obesity?

Gnant et al Lancet Oncol, 2011; Pfeiler et al, J Clin Oncol, 2011

Neoadjuvant Combined Endocrine Therapy - STAGE

Premenopausal
Receptor-positive
Her2-negative
Operable N=197

Goserelin+anastrozole +placebo (GAP)

RR 70%

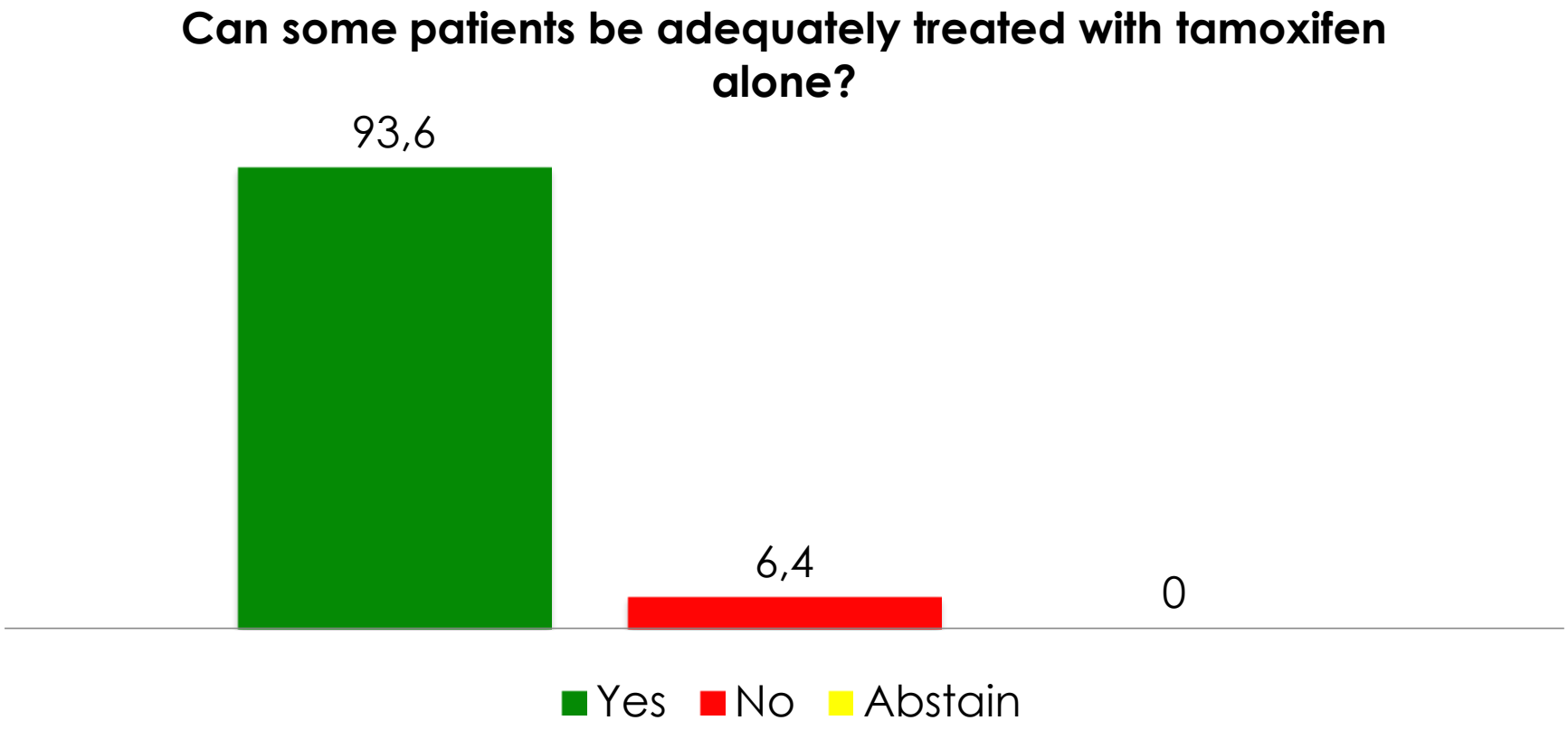
Goserelin+tamoxifen+ placebo (GTP)

RR 51%

Masuda et al, Lancet Oncol, 2012

Endocrine Therapies

Establishing Standards for Postmenopausal



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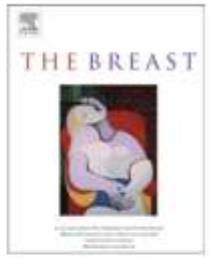


Review

Meta-analysis of breast cancer outcome and toxicity in adjuvant trials of aromatase inhibitors in postmenopausal women

Adnan Aydiner*

Istanbul University, Institute of Oncology, 34390 Istanbul, Turkey

Table 2
Effect estimates of the individual randomized controlled trials (RCTs) and the meta-analysis for AI monotherapy versus 5 yrs of tamoxifen treatment.

RCT[reference]	Intervention arm	DFS [HR (95% CI)]		OS [HR (95% CI)]		DWR [HR (95% CI)]	
		RCT	Meta-analysis	RCT	Meta-analysis	RCT	Meta-analysis
Overall,							
ATAC[18] (follow-up: 120 mo)	Anastrozole 5 yrs	0.91 (0.83–0.99)	**0.89 (0.83–0.95)** $p = 0.001$	0.97 (0.87–1.08)	**0.93 (0.83–1.03)** $p = 0.149$	0.97 (0.87–1.08)	**0.97 (0.88–1.07)** $p = 0.594$
BIG 1–98[19,20]	Letrozole 5 yrs	0.86 (0.77–0.95)		0.87 (0.76–0.99)		1.00 (0.74–1.35)	
Hormone receptor-positive							
ATAC[18] (follow-up: 120 mo)	Anastrozole 5 yrs	0.86 (0.78–0.95)	**0.86 (0.8–0.92)** $p < 0.001$	0.95 (0.85–1.06)	**0.92 (0.84–1.0)** $p = 0.046$	1.04 (0.88–1.22)	**1.03 (0.89–1.19)** $p = 0.675$
BIG 1–98[19,20]	Letrozole 5 yrs	0.86 (0.77–0.95)		0.87 (0.76–0.99)		1.00 (0.74–1.35)	

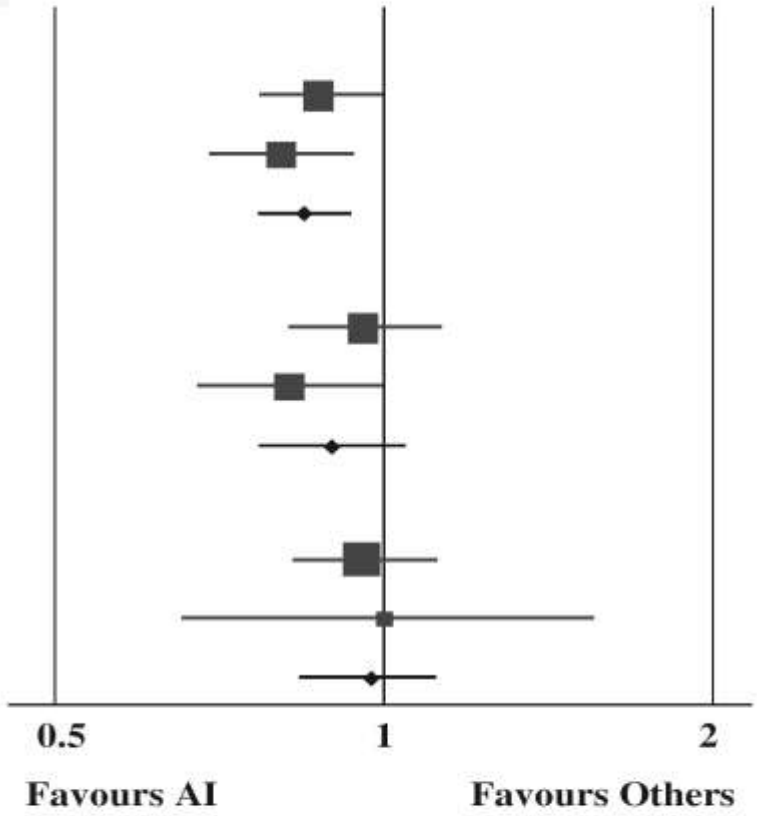
CI: confidence interval; DFS: disease-free survival; HR: hazard ratio; OS: overall survival; DWR: death without recurrence; R: receptor.

Aydiner A. The Breast, 2013

AI Monotherapy – All Pts

A

RCT reference	HR	95% CI		P
Disease-free survival				
ATAC[18]	0.91	0.83	0.99	0.036
BIG 1-98[19,20]	0.86	0.77	0.95	0.005
Meta-analysis	**0.89**	**0.83**	**0.95**	**0.001**
Overall, survival				
ATAC[18]	0.97	0.87	1.08	0.589
BIG 1-98 [19,20]	0.87	0.76	0.99	0.042
Meta-analysis	**0.93**	**0.83**	**1.03**	**0.149**
Death without recurrence				
ATAC[18]	0.97	0.87	1.08	0.568
BIG 1-98[19,20]	1.00	0.74	1.35	0.989
Meta-analysis	**0.97**	**0.88**	**1.07**	**0.594**



RCT: randomized controlled trial; HR: hazard ratio; 95% CI: lower and upper boundaries of the 95% confidence interval; AI: aromatase inhibitor

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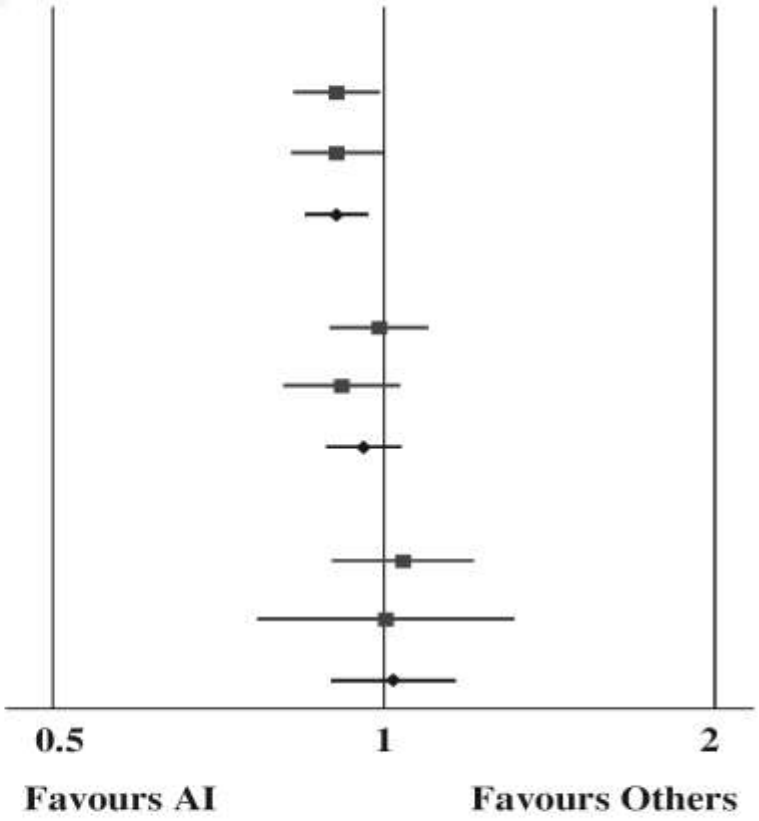
AI Monotherapy – HR (+) Pts

B

RCT [reference]	HR	95% CI		P
Disease-free survival				
ATAC[18]	0.86	0.78	0.95	0.003
BIG 1-98[19,20]	0.86	0.77	0.95	0.005
Meta-analysis	**0.86**	**0.80**	**0.92**	**<0.001**
Overall survival				
ATAC[18]	0.95	0.85	1.06	0.373
BIG 1-98[19,20]	0.87	0.76	0.99	0.042
Meta-analysis	**0.92**	**0.84**	**1.00**	**0.046**
Death without recurrence				
ATAC[18]	1.04	0.88	1.22	0.638
BIG 1-98[19,20]	1.00	0.74	1.35	0.989
Meta-analysis	**1.03**	**0.89**	**1.19**	**0.675**



RCT: randomized controlled trial; HR: hazard ratio; 95% CI: lower and upper boundaries of the 95% confidence interval; AI: aromatase inhibitor

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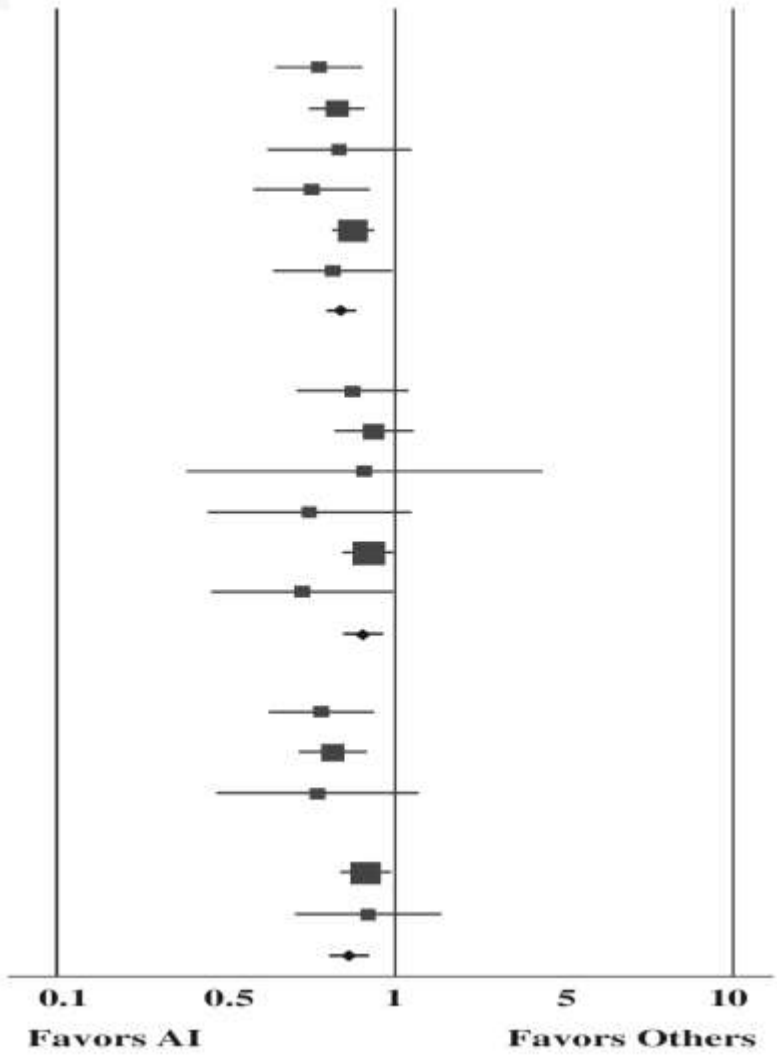
Sequenced AI Therapy – All Pts

RCT reference	HR	95% CI		P
Disease-free survival				
ABCSG 8+ ARNO-95 [13]	0.60	0.44	0.81	0.001
TEAM [16]	0.68	0.56	0.82	<0.001
N-SAS BC03 [17]	0.69	0.42	1.14	0.145
ITA [14]	0.57	0.38	0.85	0.006
IE Study [12]	0.76	0.66	0.88	<0.001
ARNO 95 [13,21]	0.66	0.44	0.99	0.047
Meta-analysis	**0.70**	**0.63**	**0.77**	**<0.001**
Overall, survival				
ABCSG 8+ ARNO-95 [13]	0.76	0.51	1.12	0.160
TEAM [16]	0.88	0.67	1.16	0.361
N-SAS BC03 [17]	0.82	0.24	2.84	0.757
ITA [14]	0.56	0.28	1.13	0.108
IE Study [12]	0.85	0.71	1.02	0.079
ARNO 95 [13,21]	0.53	0.28	1.00	0.049
Meta-analysis	**0.81**	**0.71**	**0.93**	**0.003**
Distant metastasis				
ABCSG 8+ ARNO-95 [13]	0.61	0.42	0.88	0.008
TEAM [16]	0.66	0.52	0.83	<0.001
N-SAS BC03 [17]	0.59	0.29	1.20	0.146
ITA [14]	--	--	--	--
IE Study [12]	0.83	0.70	0.98	0.031
ARNO 95 [13,21]	0.84	0.51	1.40	0.511
Meta-analysis	**0.74**	**0.65**	**0.85**	**<0.001**



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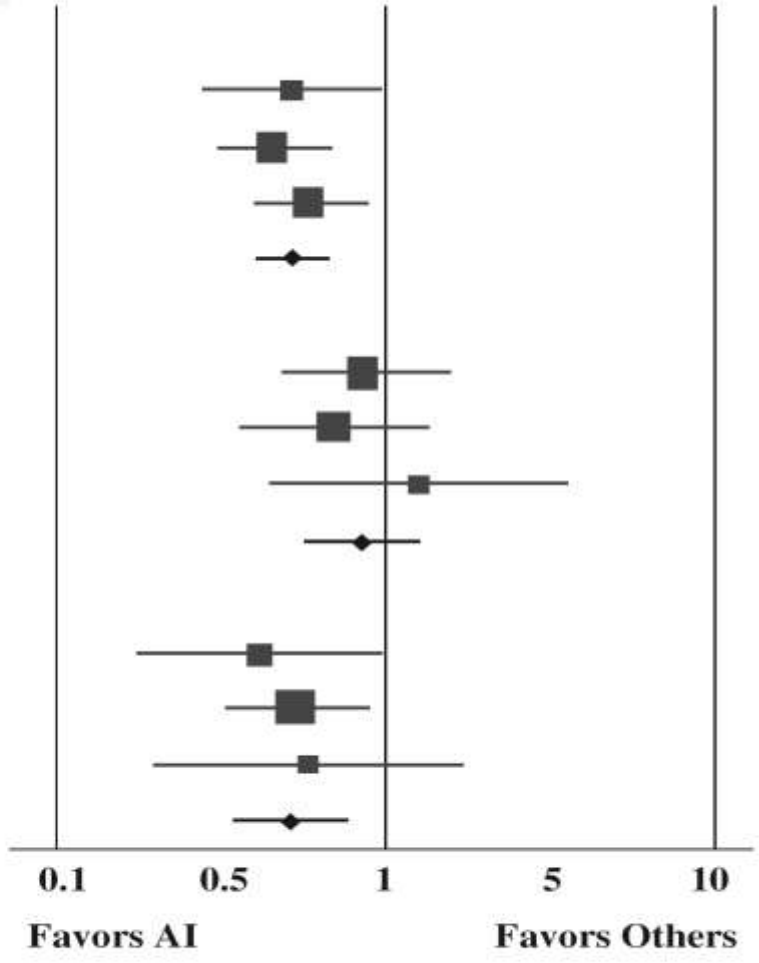
Extended AI Therapy – All Pts

RCT [reference]	HR	95% CI		P
Disease-free survival				
ABCSG 6a [25]	0.62	0.40	0.96	0.032
MA.17 [22,23]	0.57	0.43	0.75	<0.001
NSABP B-33 [24]	0.68	0.51	0.90	0.007
Meta-analysis	**0.62**	**0.52**	**0.74**	**<0.001**
Overall, survival				
ABCSG 6a [25]	0.89	0.59	1.34	0.578
MA.17 [22,23]	0.76	0.48	1.21	0.245
NSABP B-33 [24]	1.15	0.55	2.38	0.709
Meta-analysis	**0.87**	**0.66**	**1.16**	**0.342**
Distant metastasis				
ABCSG 6a [25]	0.53	0.29	0.96	0.038
MA.17 [22,23]	0.64	0.45	0.91	0.013
NSABP B-33 [24]	0.67	0.32	1.43	0.300
Meta-analysis	**0.62**	**0.46**	**0.82**	**0.001**



RCT: randomized controlled trial; HR: hazard ratio: 95% CI: lower and upper boundaries of the 95% confidence interval; AI: aromatase inhibitor

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Conclusions

- DFS was significantly improved by AI monotherapy, sequenced therapy and extended therapy.
- All of the patients benefited significantly from sequenced therapy,
- Hormone receptor positive patients benefited from AI monotherapy with respect to OS
- Safety analyses
  - AI monotherapy conferred significantly lower risks for thromboembolic events and endometrial cancer compared with tamoxifen monotherapy; however, **there was a greater risk of cardiovascular events.**
  - Sequenced therapy was also superior in terms of endometrial cancer but was inferior with respect to fractures, thromboembolic and cardiovascular events.

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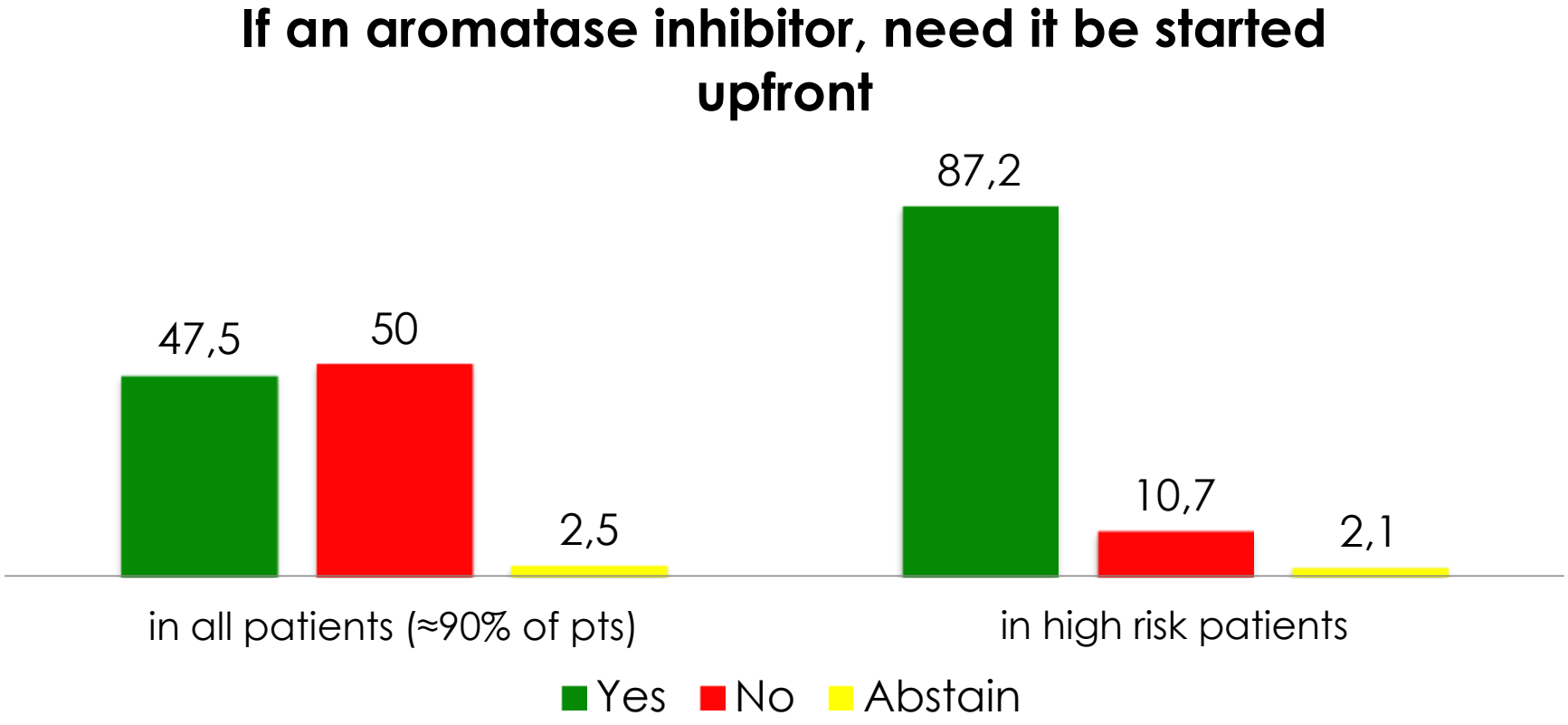
Endocrine Therapies

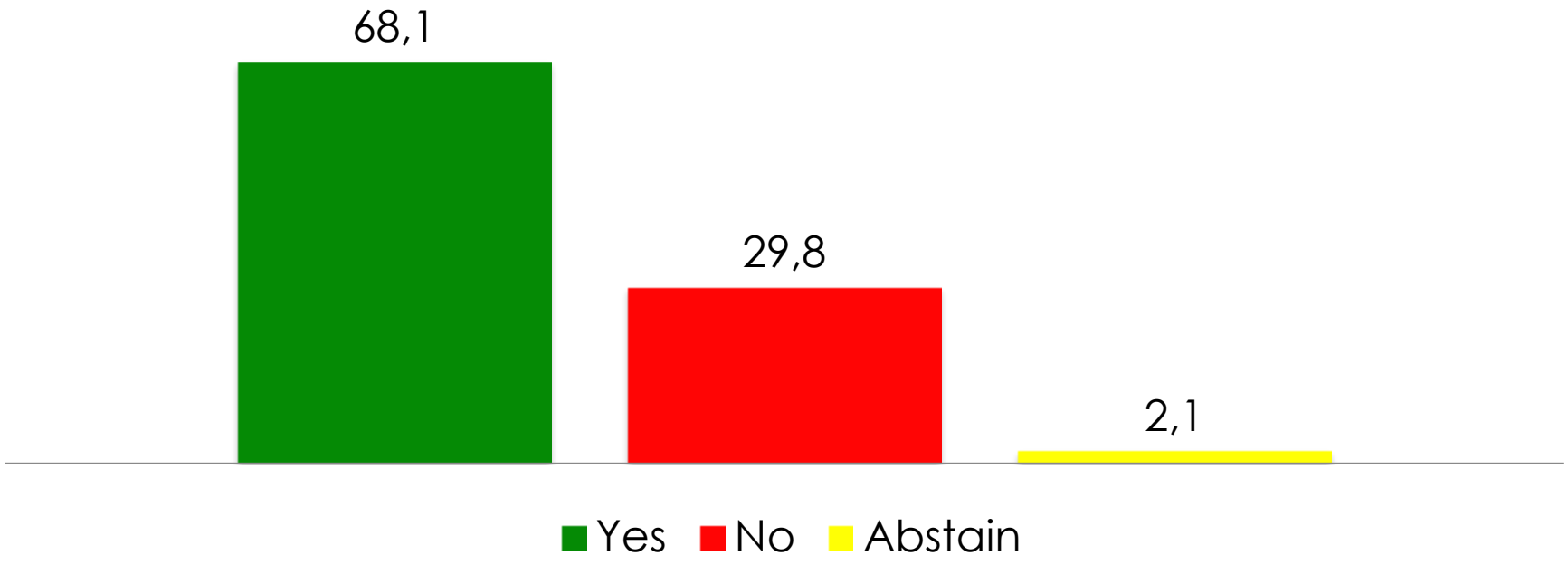
Establishing Standards for Postmenopausal



Endocrine Therapies

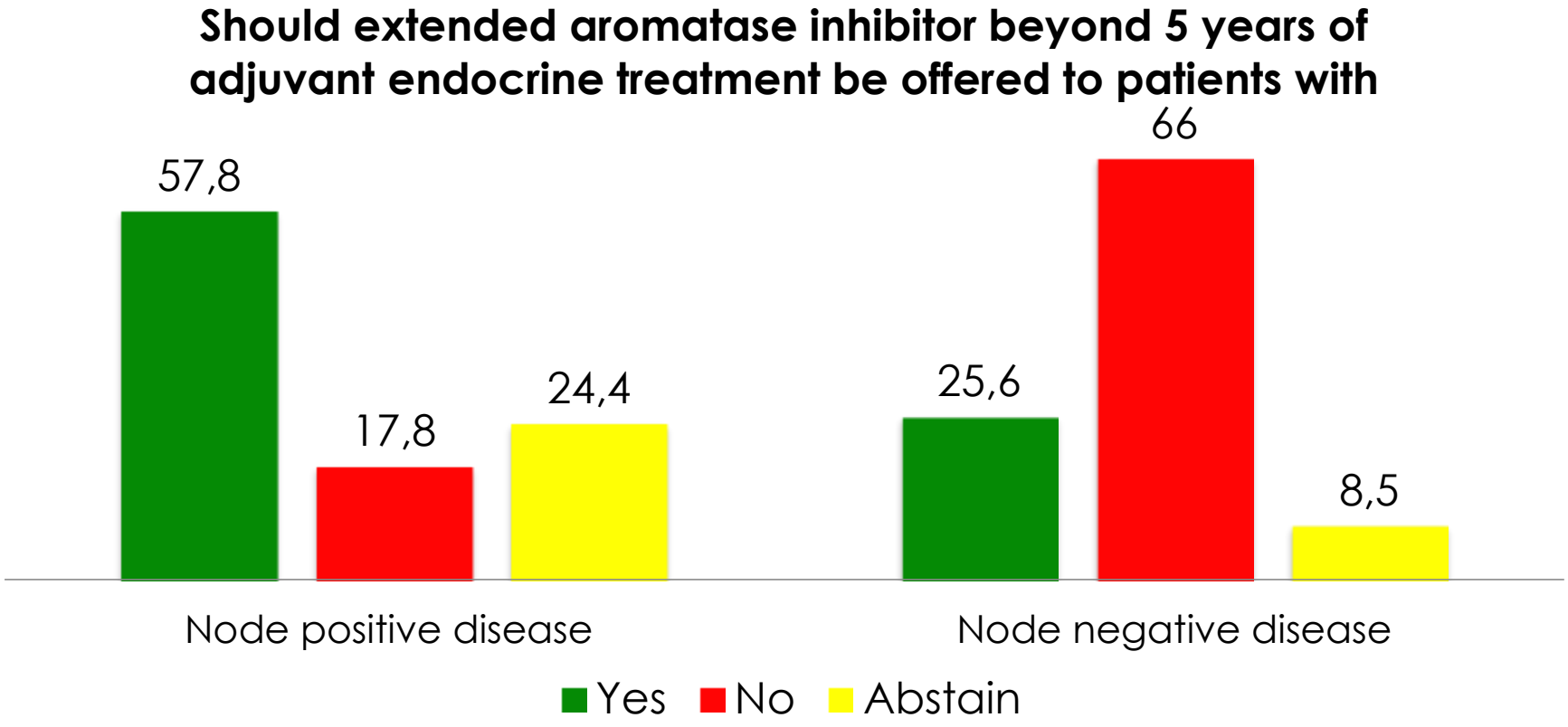
Establishing Standards for Postmenopausal

Can upfront aromatase inhibitor be replaced with tamoxifen after 2 years?



Endocrine Therapies

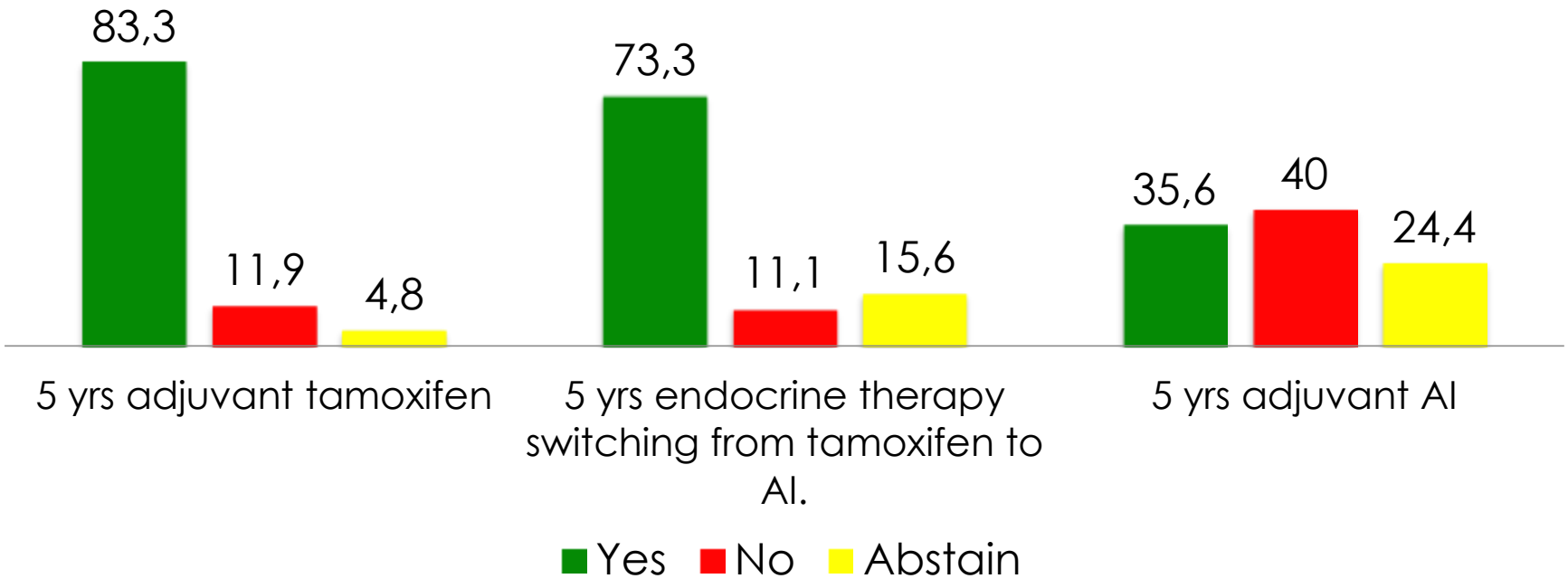
Establishing Standards for Postmenopausal



Endocrine Therapies

Establishing Standards for Postmenopausal

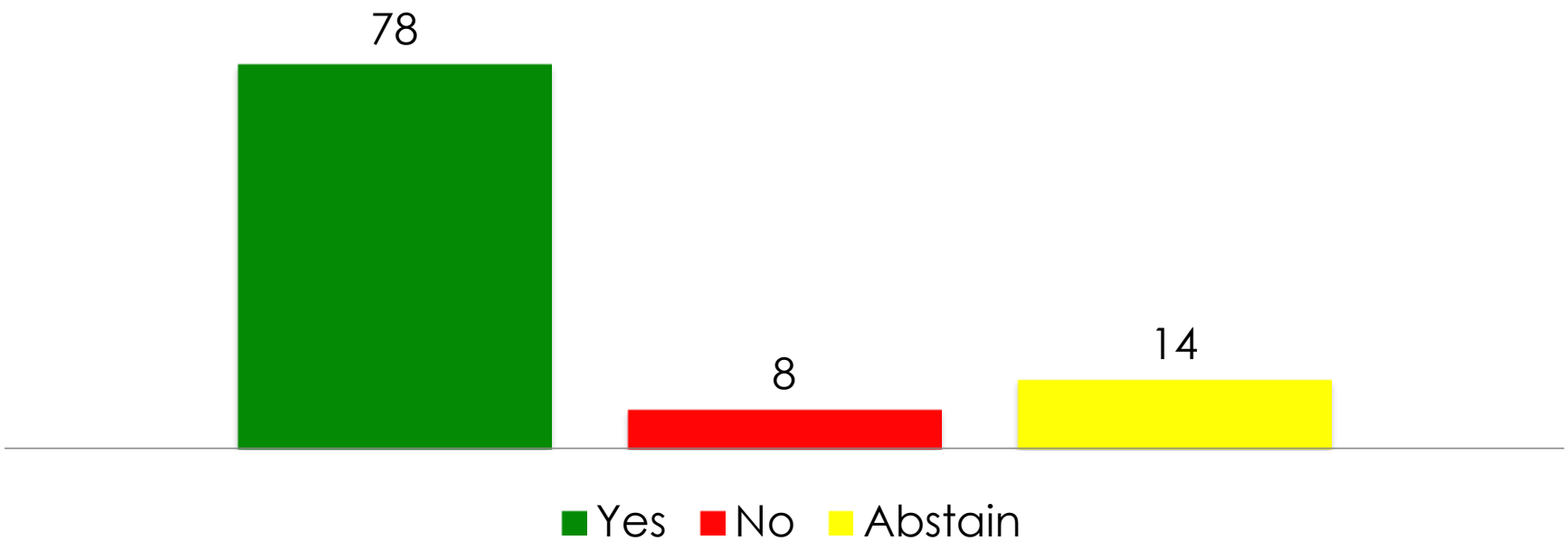
If so, does prior endocrine therapy matter? Should extend AI beyond 5 years be given after:



Endocrine Therapies

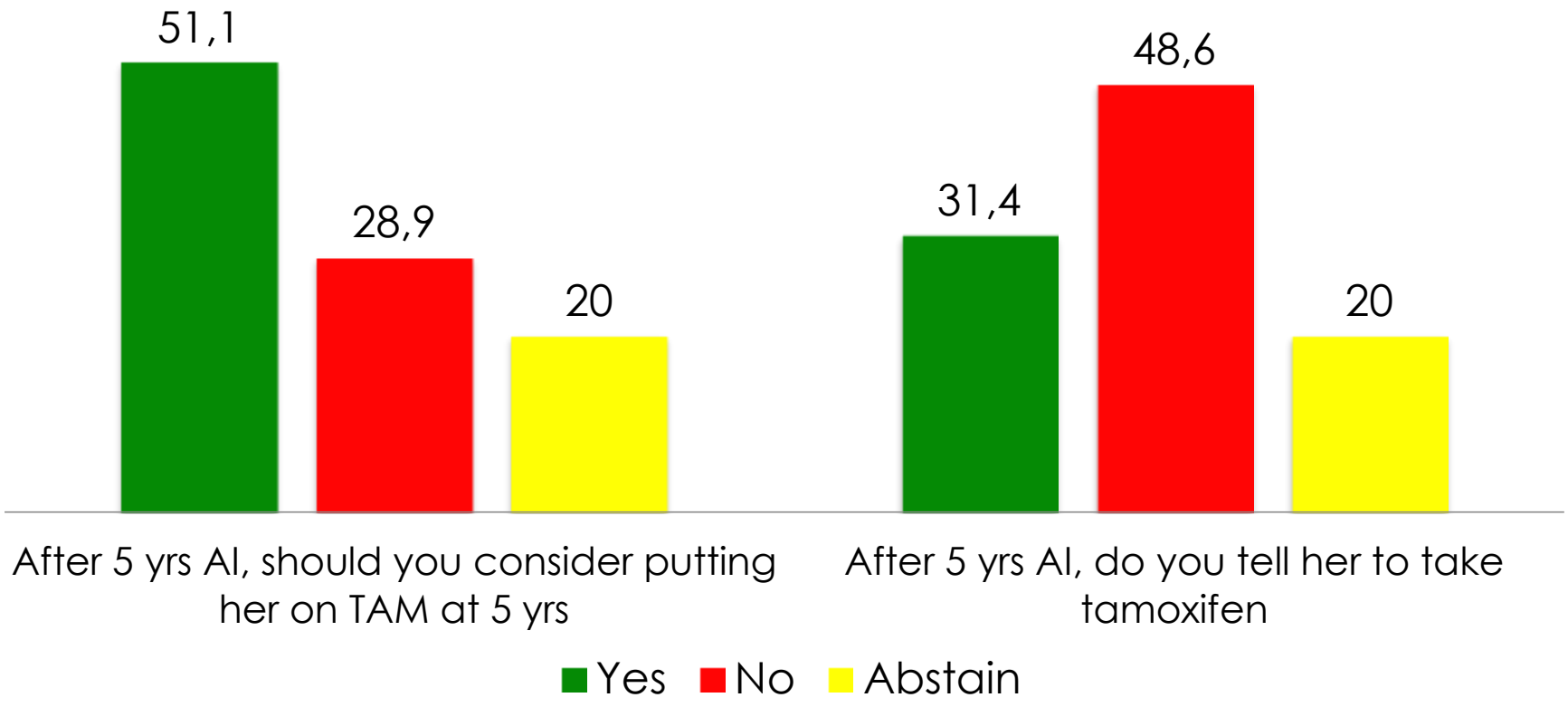
Establishing Standards for Postmenopausal

If AI is unavailable or not tolerated (to switch to tamoxifen), should tamoxifen be continued beyond 5 years.



Endocrine Therapies

Establishing Standards for Postmenopausal



consensus

ENDOCRINE THERAPIES

- Tamoxifen as default (in ER +)
- Tamoxifen duration should be extended to 10 years in some patients remaining premenopausal
- Ovarian function supression (OFS) should not be added to tamoxifen in all patients, may be added in the young (eg < 40).
- Aİ+OFS is a valid option in case of contraindication to tamoxifen

consensus

ENDOCRINE THERAPIES
Postmenopausal

- Some patients can be adequately treated with tamoxifen alone.
- If an aromatase inhibitor, it needs to be started upfront in high risk patients
- Upfront aromatase inhibitor can be replaced with tamoxifen after 2 years

consensus

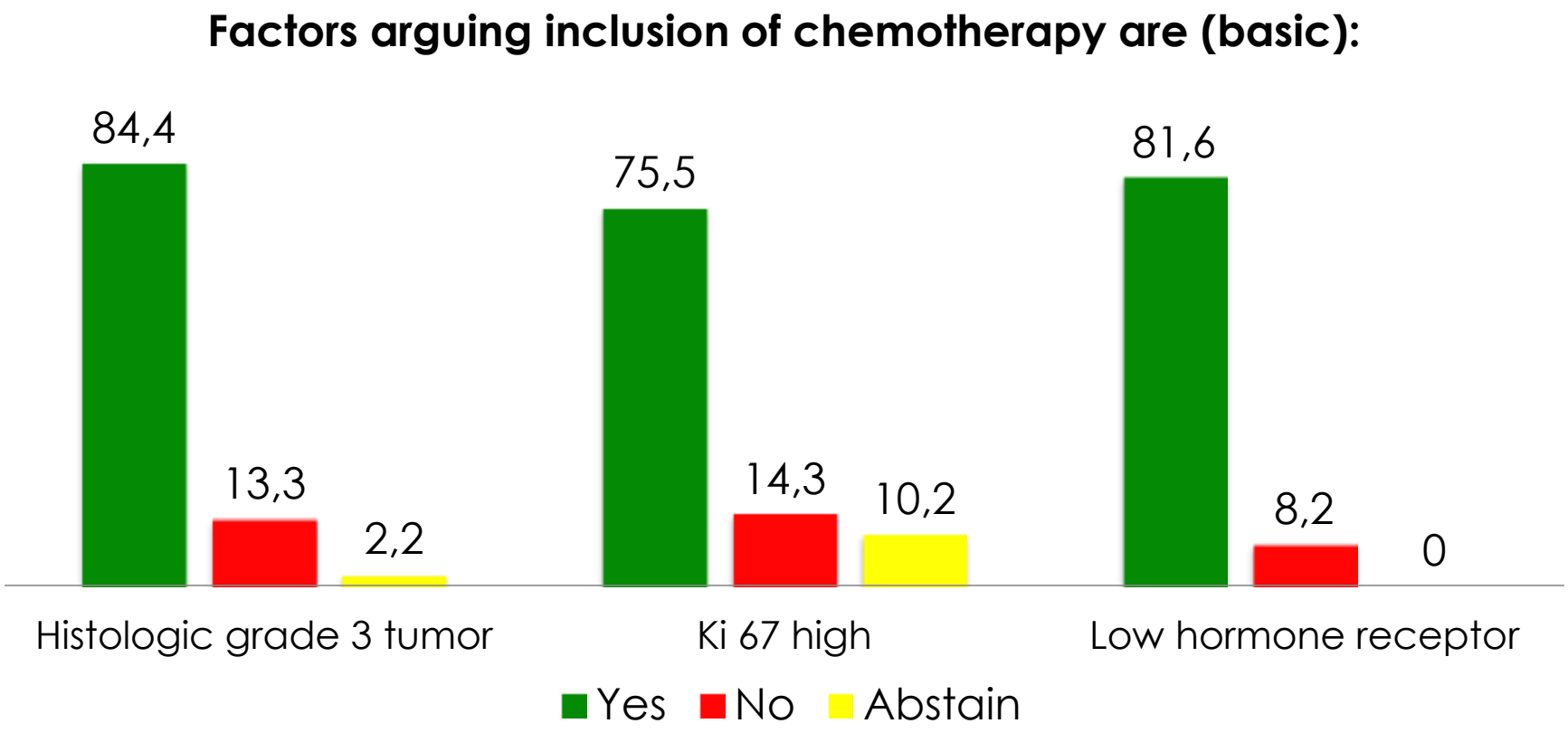
ENDOCRINE THERAPIES

- Extended aromatase inhibitor beyond 5 years of adjuvant endocrine treatment should be offered to patients with node positive disease
- If AI is unavailable or not tolerated (to switch to tamoxifen), tamoxifen should be continued beyond 5 years
- After 5 yrs AI, tamoxifen should be considered any time

Conference Topic

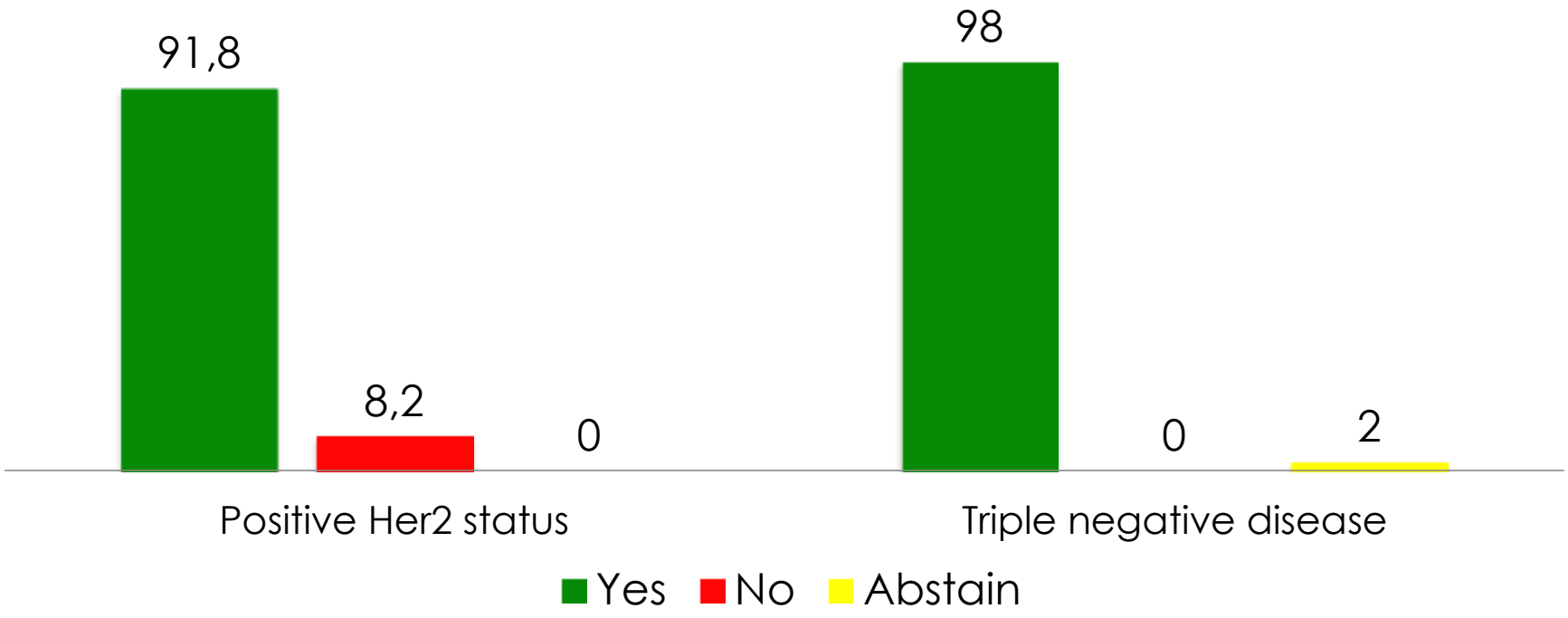
Chemotherapy

Chemotherapy

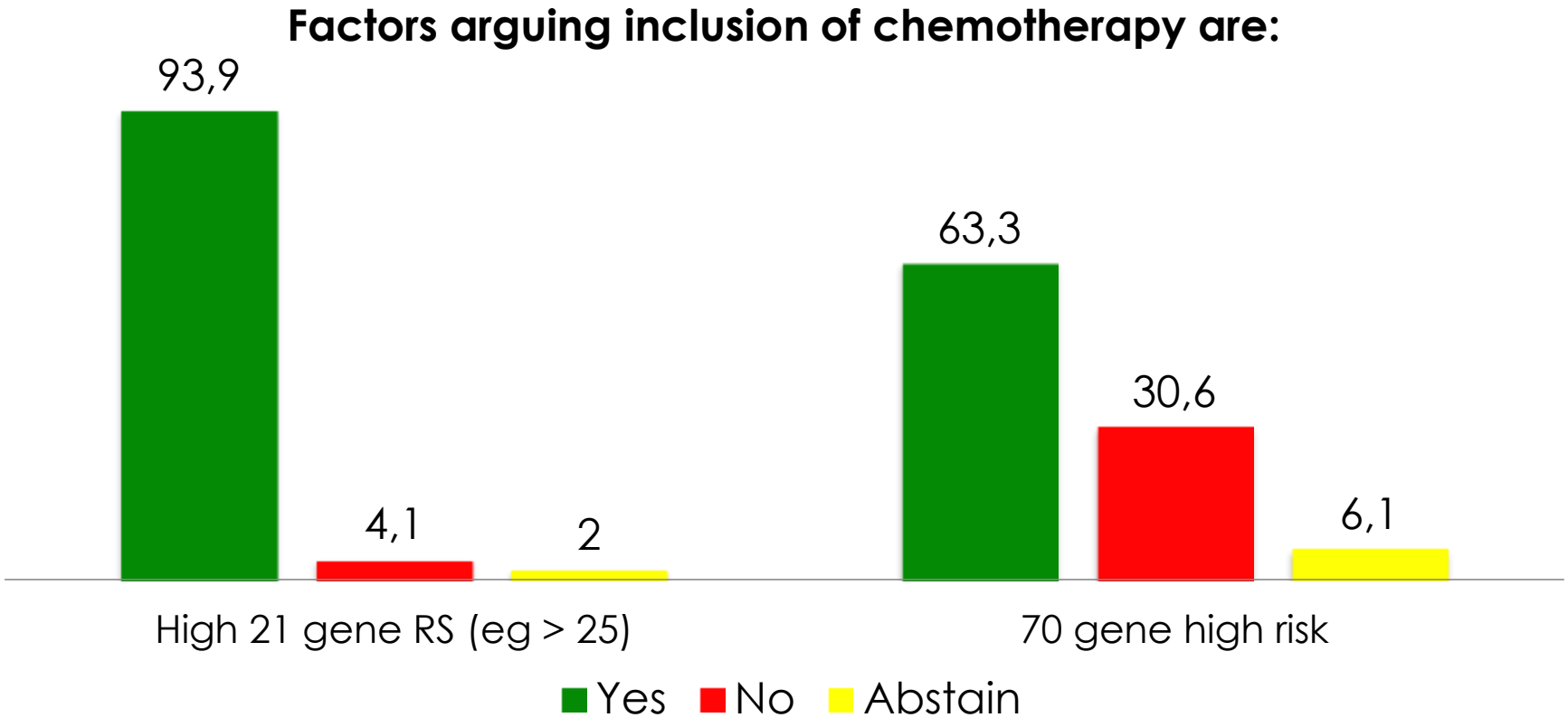


Chemotherapy

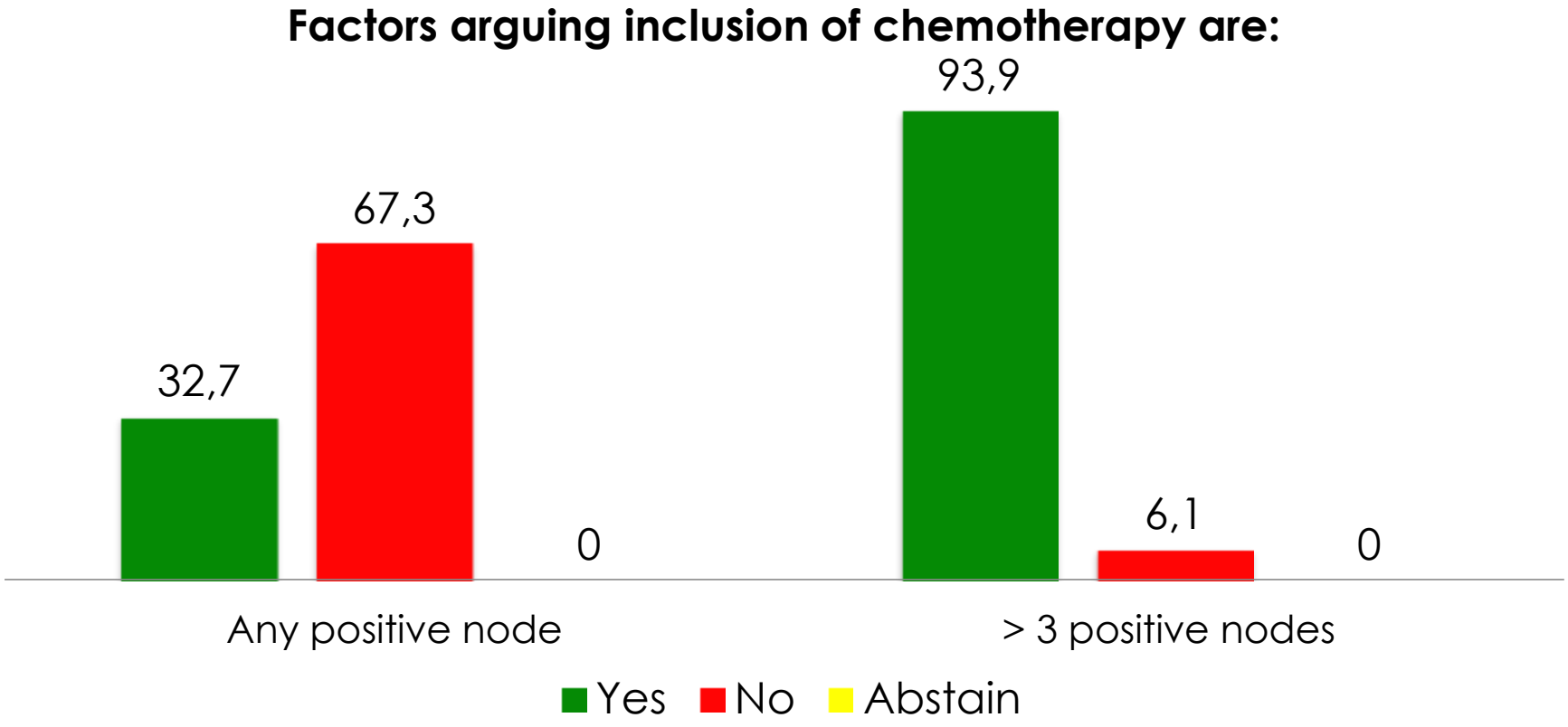
Factors arguing inclusion of chemotherapy are (basic):



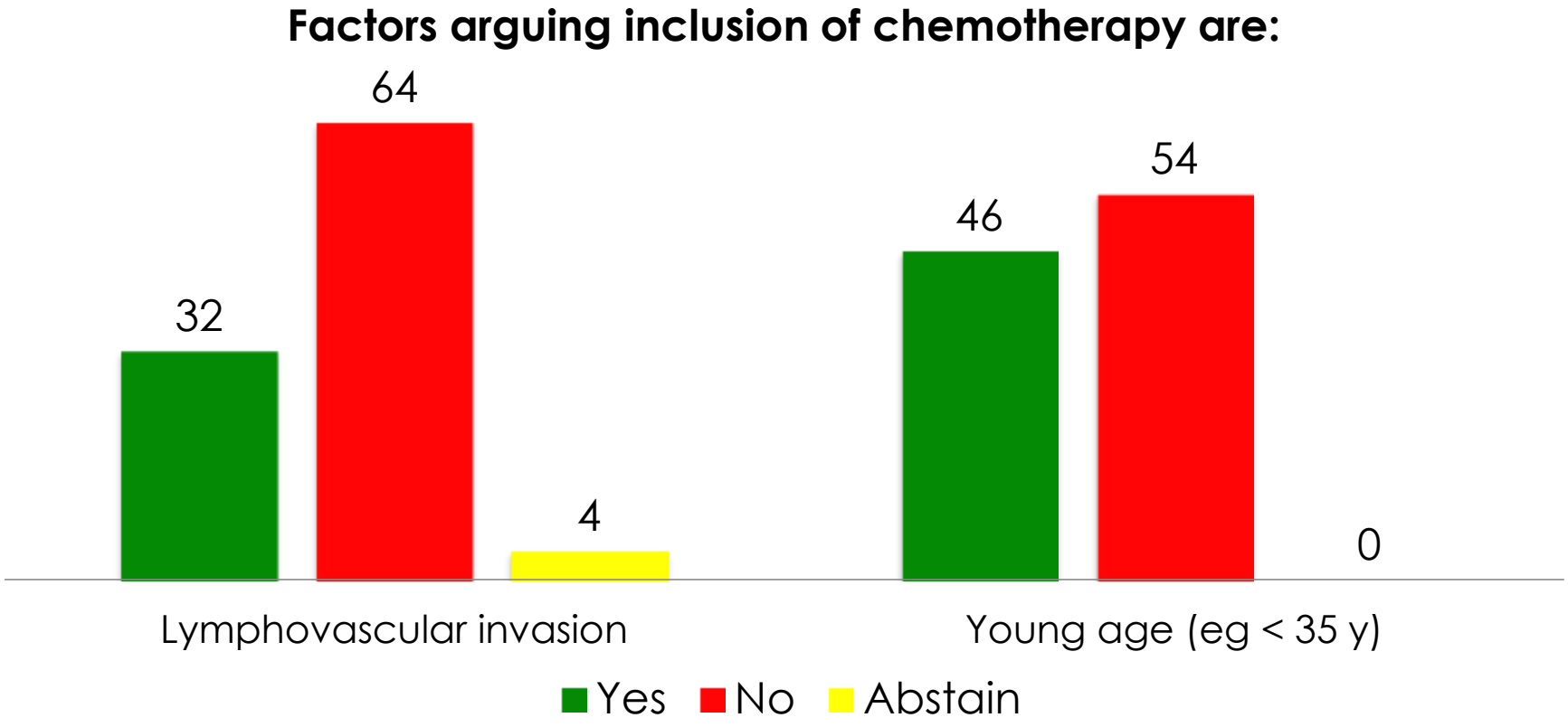
Chemotherapy



Chemotherapy



Chemotherapy



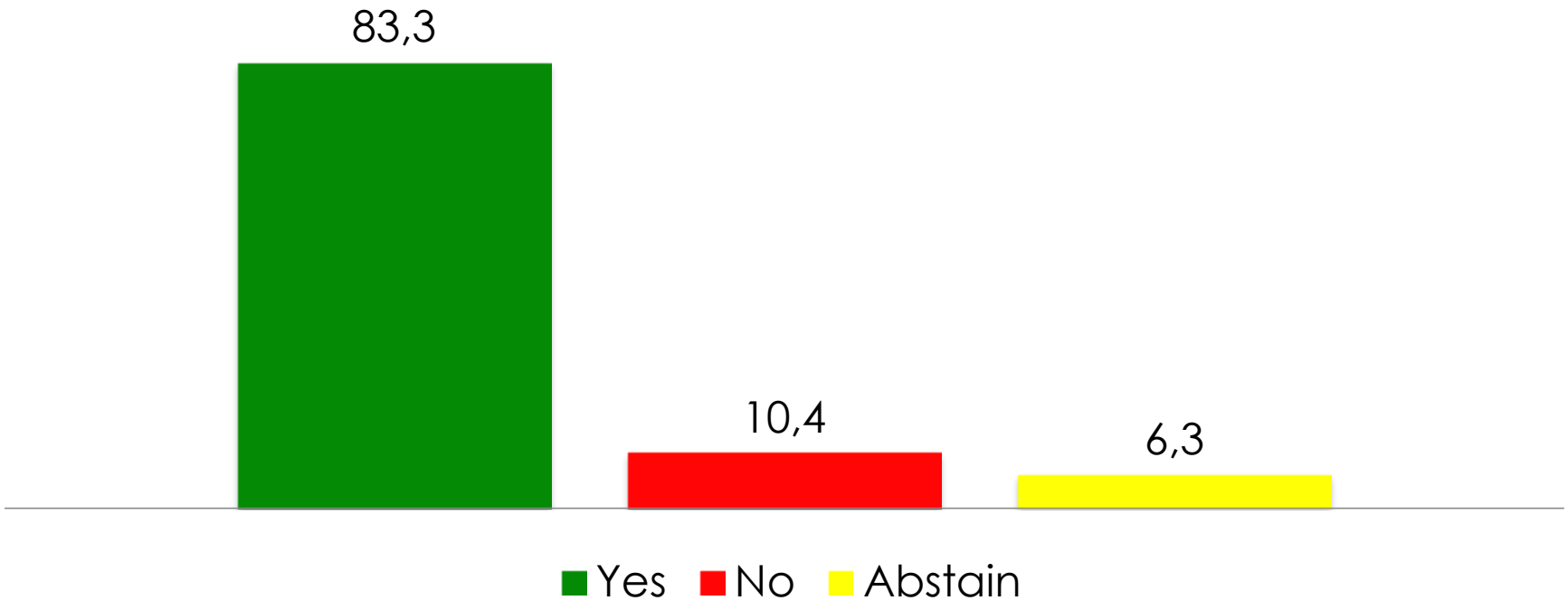
consensus

CHEMOTHERAPY

- Factors arguing inclusion of chemotherapy are:
  - histologic grade 3 tumor,
  - high Ki67,
  - low ER,
  - positive Her2 status,
  - triple negative disease,
  - high 21 gene RS (eg > 25)
  - ≥ 4 positive nodes

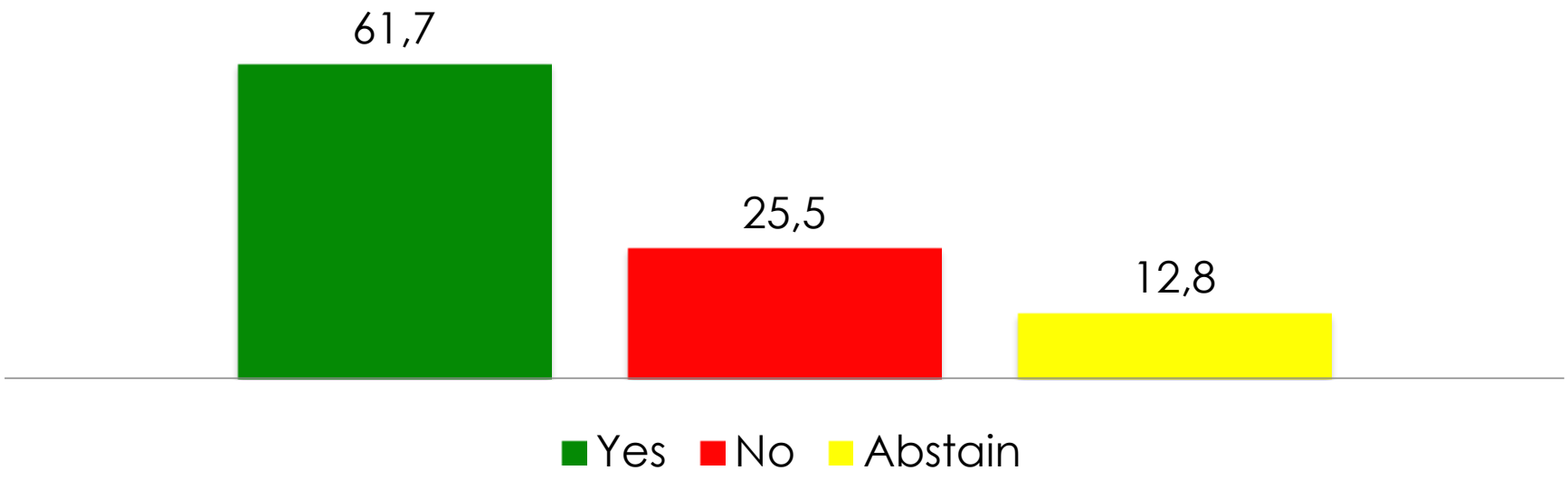
Chemotherapy

Is luminal A phenotype less responsive to CT?

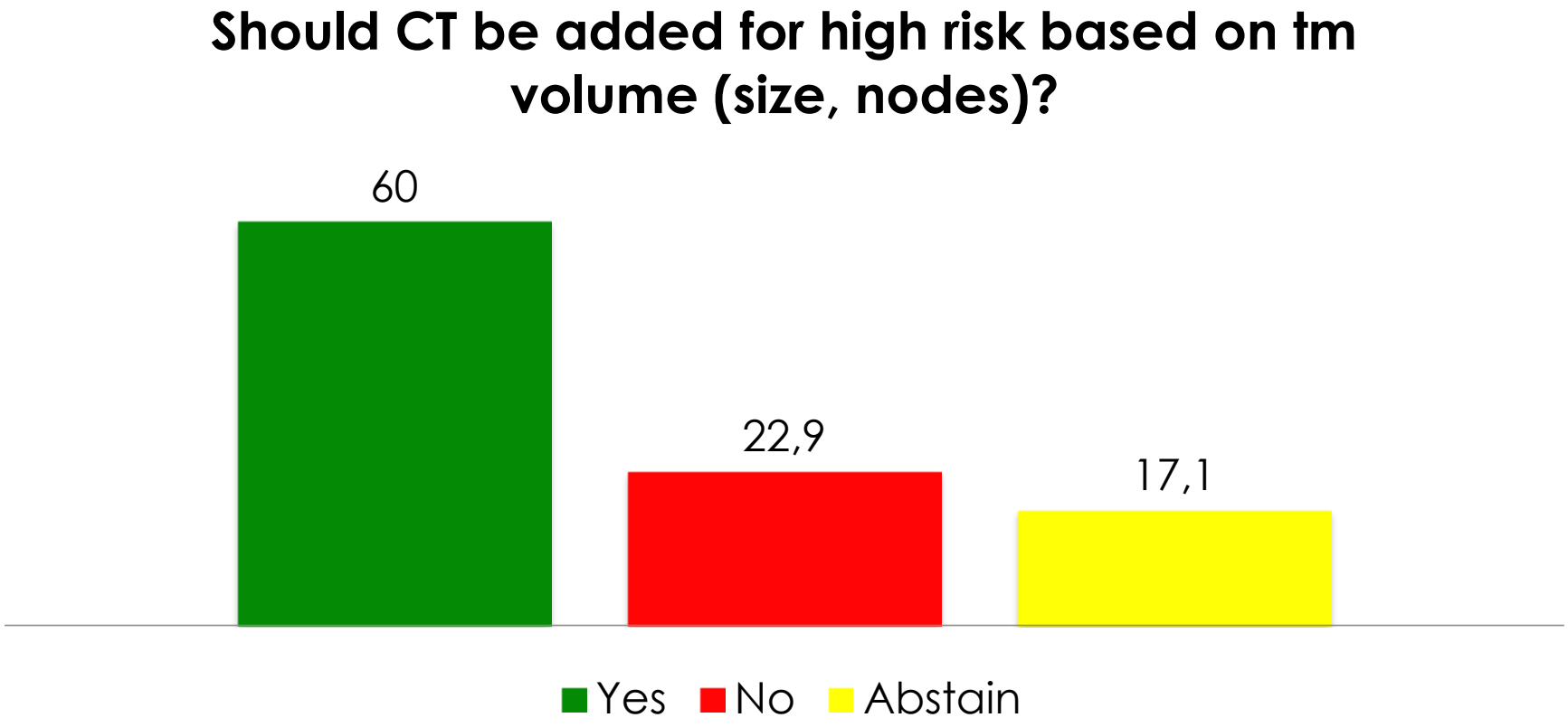


Chemotherapy

Is less intensive CT such as AC4 or CMF 6 or TC4 adequate if CT is considered in Luminal A disease?



Chemotherapy



Systemic treatment recommendations

'Subtype'	Type of therapy	Notes
'Luminal A'	Endocrine therapy alone	Few require cytotoxics (e.g. high nodal status).
'Luminal B (HER2 negative)'	Cytotoxics + endocrine therapy	Inclusion and type of cytotoxics may depend on level of endocrine expression, perceived risk and patient preference.
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2+ endocrine therapy	No data are available to support the omissionof cytotoxics in this group.
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2	Patients at very low risk may be observed without treatment
'Triple negative (ductal)'	Cytotoxics	
'Special histological types'*		
A. Endocrine responsive	Endocrine therapy	
B. Endocrine non responsive	Cytotoxics	Medullary and apocrine carcinomas may not require any adjuvant cytotoxics (if node negative).

Goldhirsch A. Annals Oncol 2011, doi:10.1093/annonc/mdr304

More Data for Selecting TYPE of Adjuvant Chemotherapy for ER+ "Luminal" Breast Cancer

- **Central IHC for ER, HER2 – CALGB 9344**
  No benefit to paclitaxel after AC (vs AC) if ER+/HER2-

- **Central IHC for ER, HER2, Ki67 – BCIRG 001**
  No benefit to TAC (vs FAC) if ER+/HER2-/Ki67 low

- **PAM50 – NCIC MA.5**
  No benefit to CEF (Vs CMF) in either Luminal A or Luminal B

- **ClinPath, PAM50, PAM50 proliferation – GEICAM 9906**
  Benefit to paclitaxel after FEC (vs FEC only low PAM50 proliferation

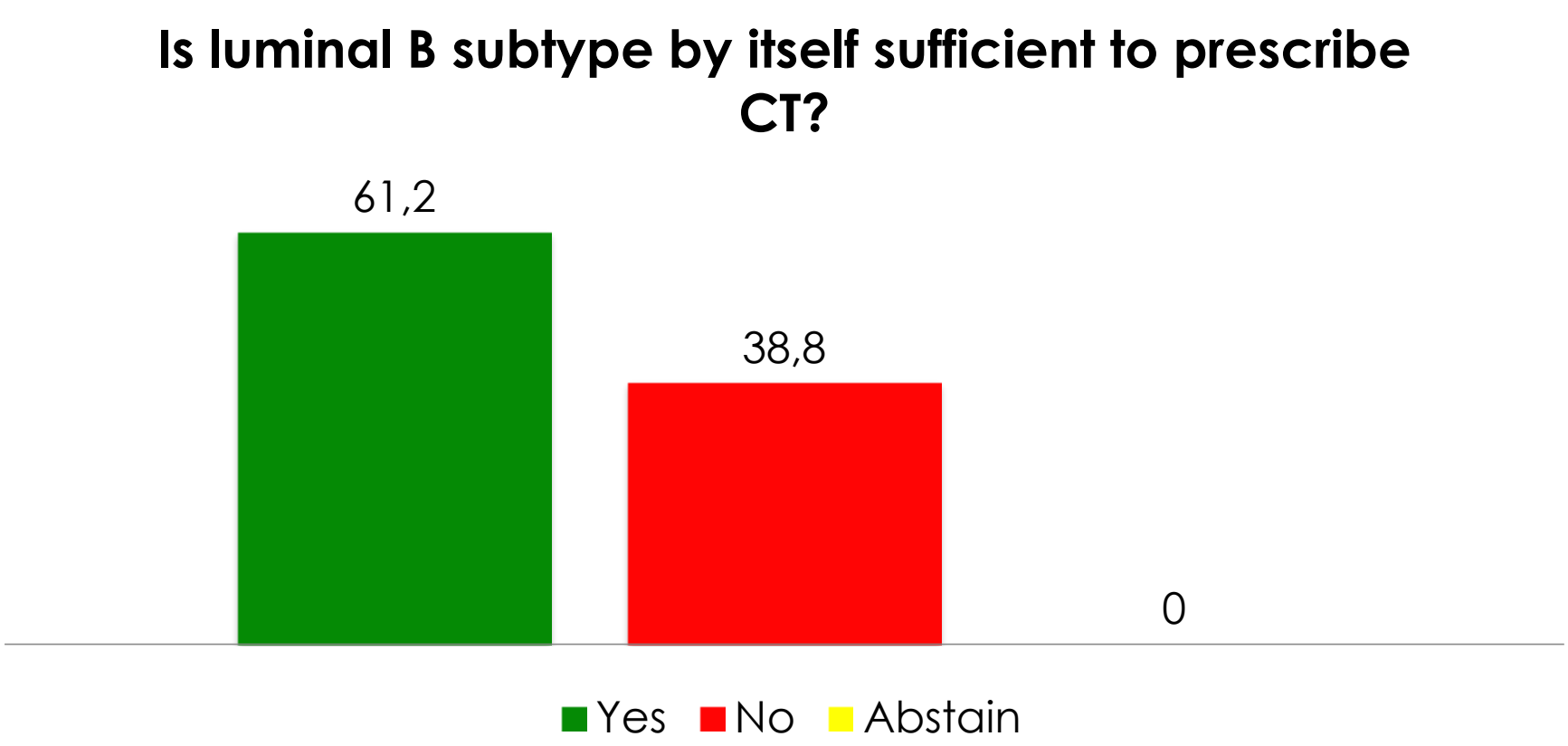
Albain KS, St Gallen 2013

consensus

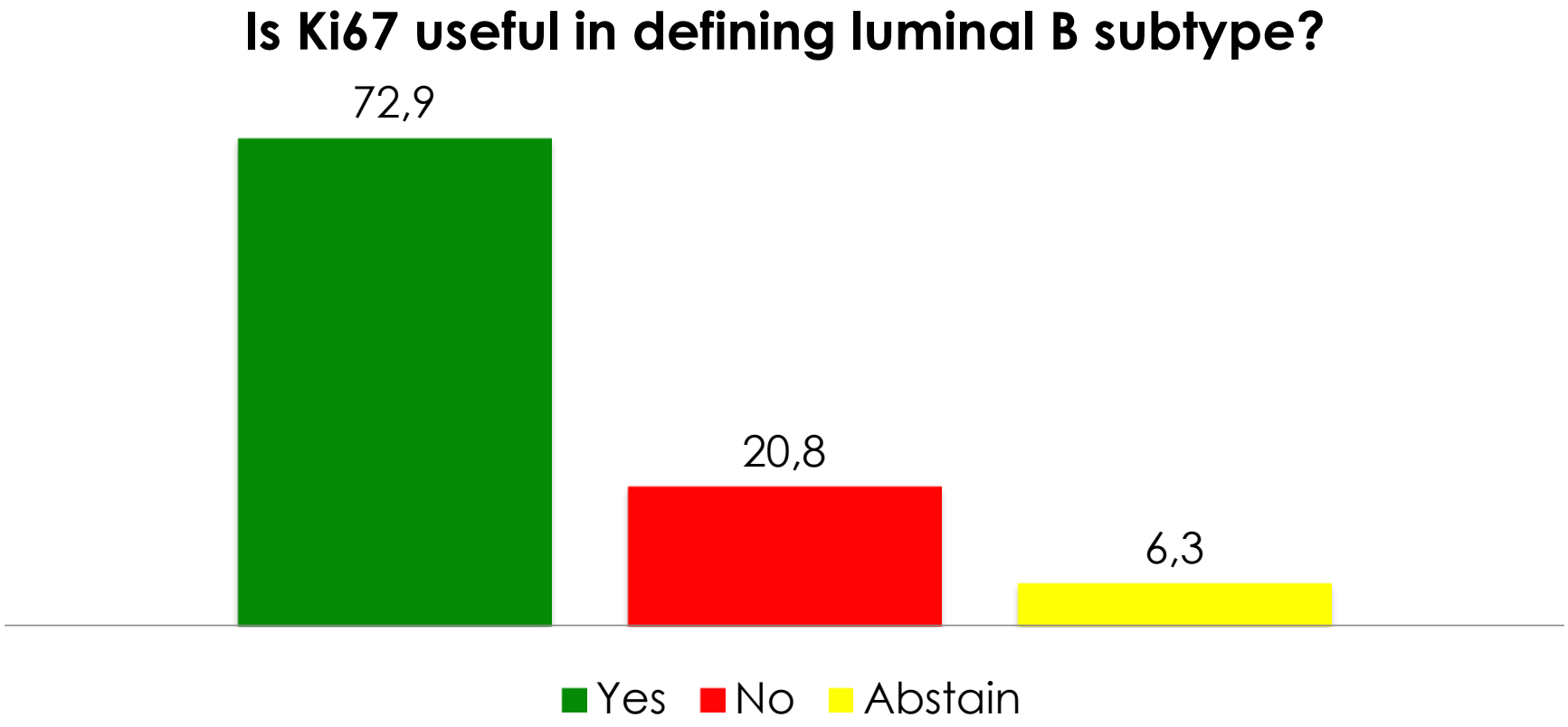
CHEMOTHERAPY
Luminal A

- Luminal A phenotype is less responsive to CT
- Less intensive CT, such as AC4 or CMF 6 or TC4 are adequate if CT is considered in Luminal A disease
- CT should be added for high risk based on tm volume (e.g. size, nodes)

Chemotherapy
Luminal B HER2 (-)

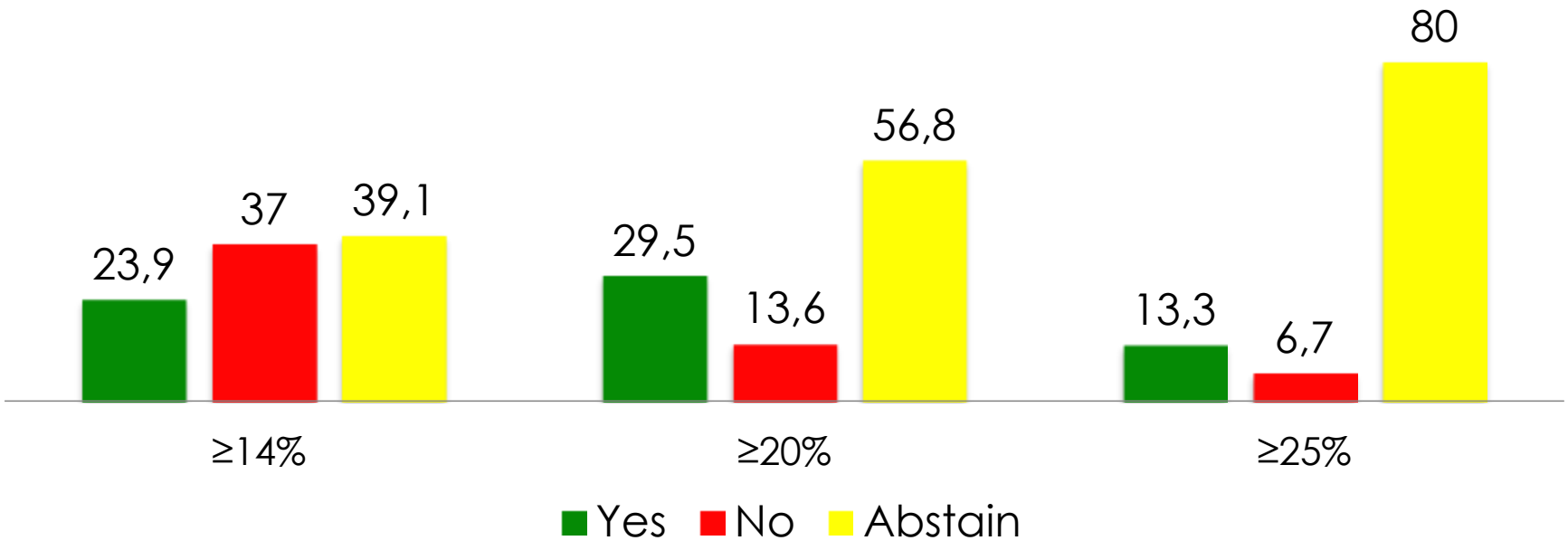


Chemotherapy
Luminal B HER2 (-)



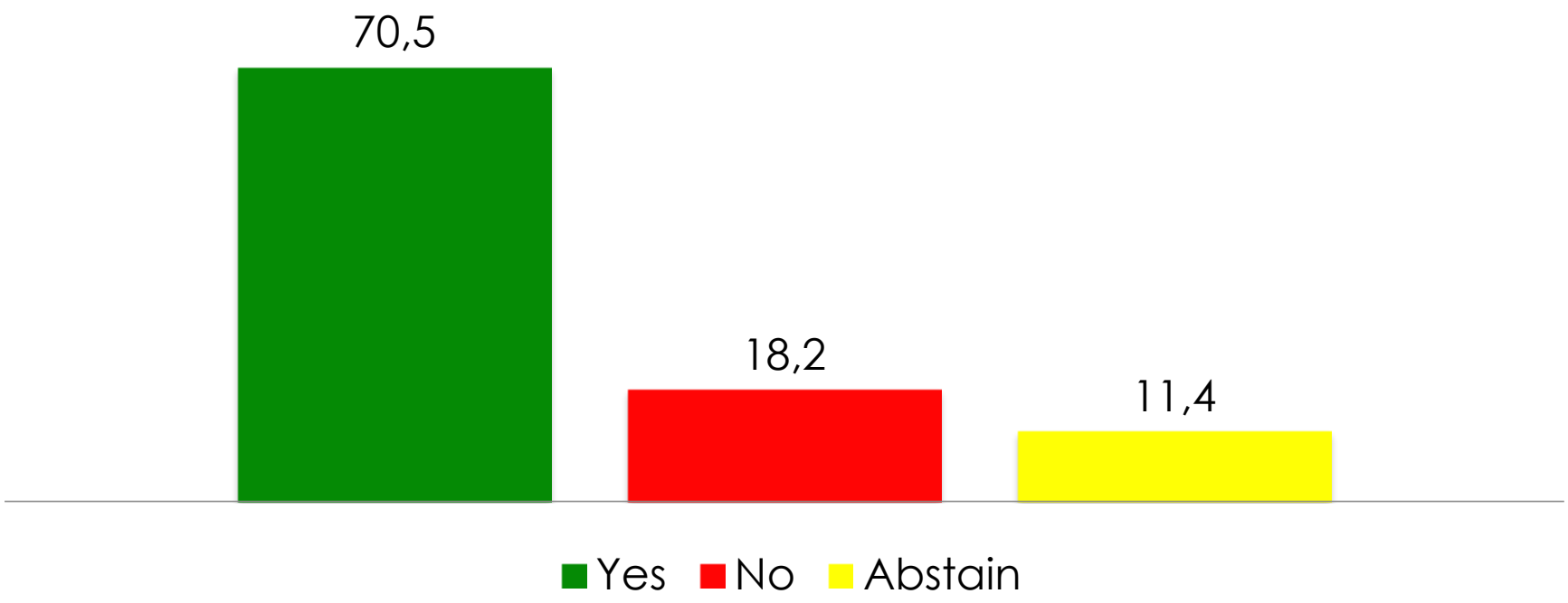
Chemotherapy
Luminal B HER2 (-)

If Ki67 is used, which thresold should be used for defining luminal B subtype (Her 2 -)?

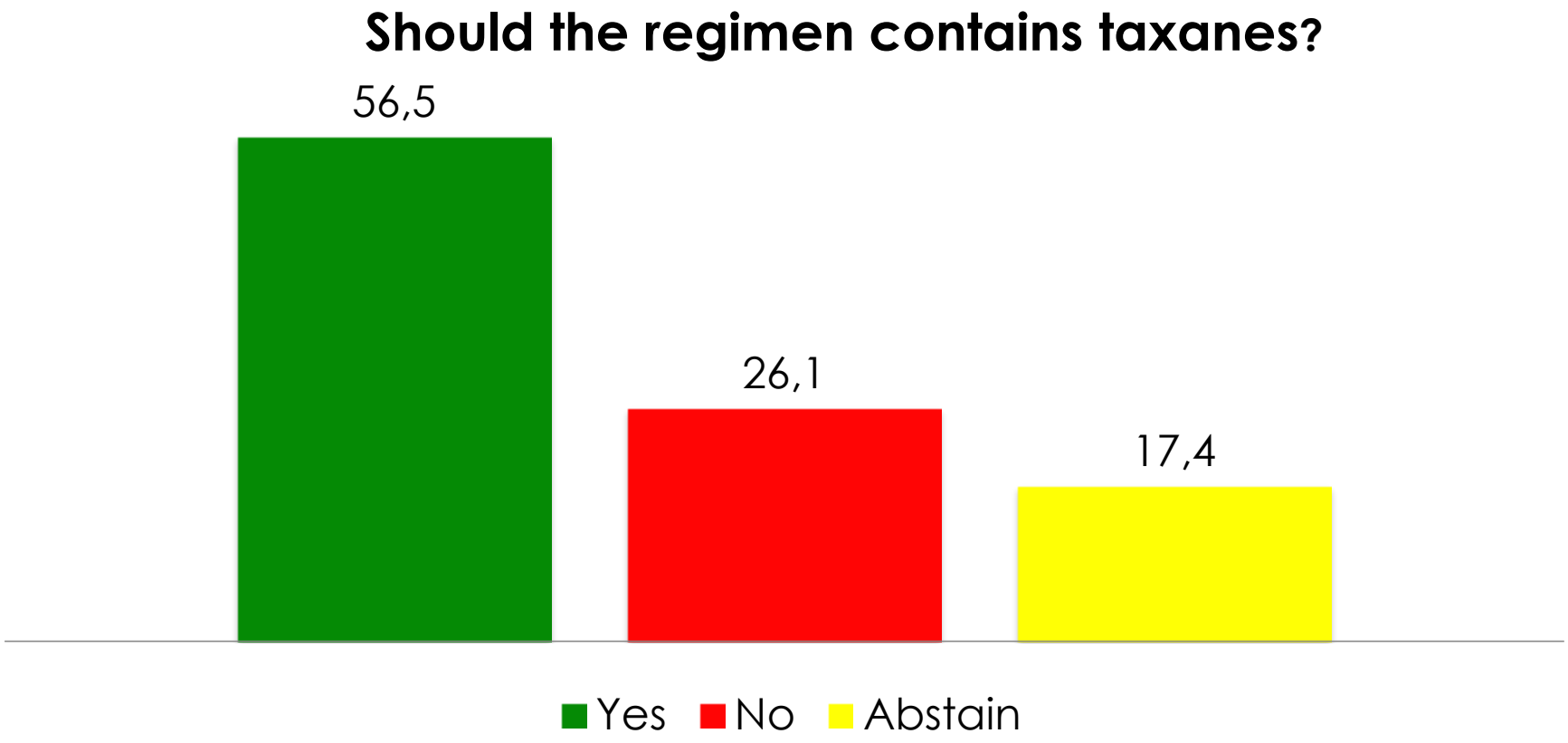


Chemotherapy
Luminal B HER2 (-)

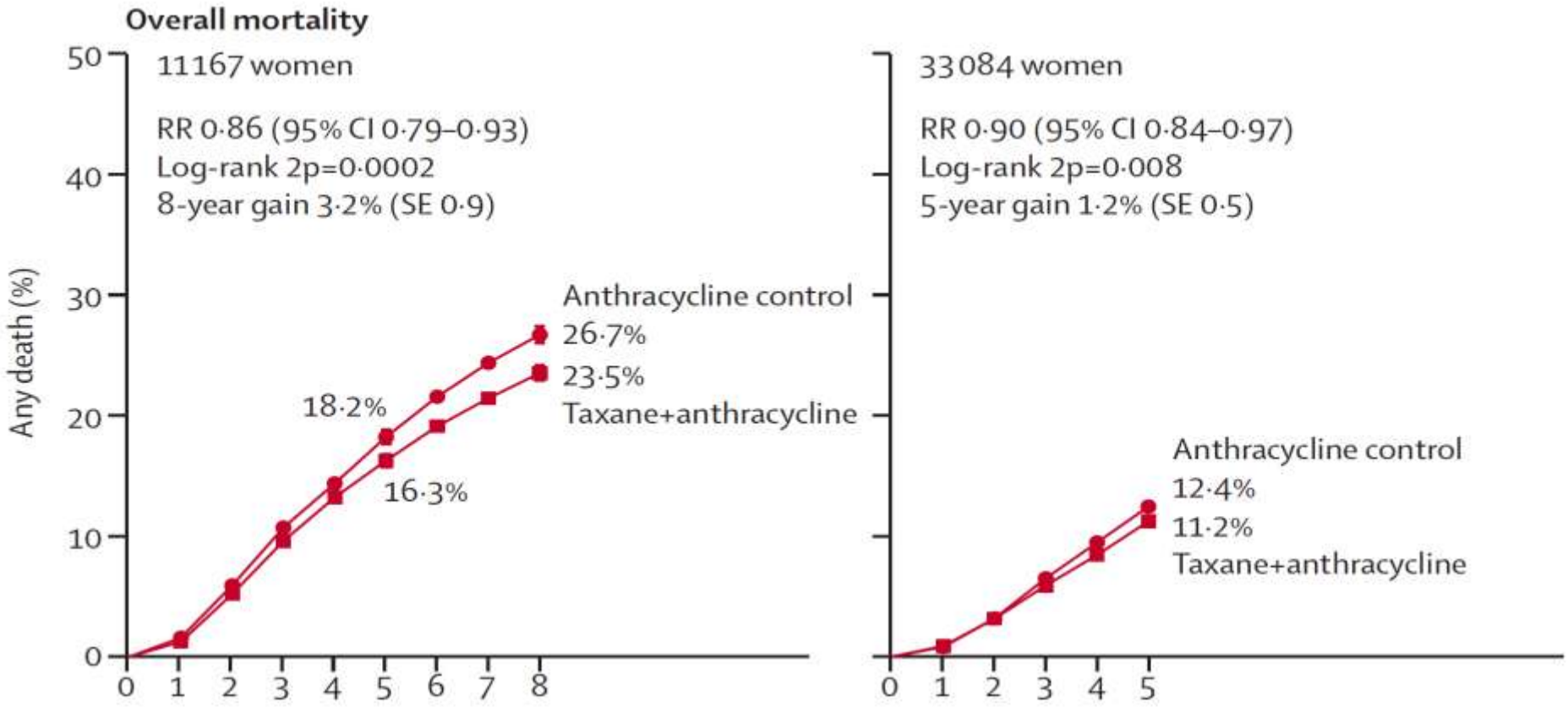
If given CT regimen should contain antracycline rather than CMF?



Chemotherapy
Luminal B HER2 (-)



Early Breast Cancer Trialists' Collaborative Group (EBCTCG)



Lancet. 2012 February 4; 379(9814): 432–444

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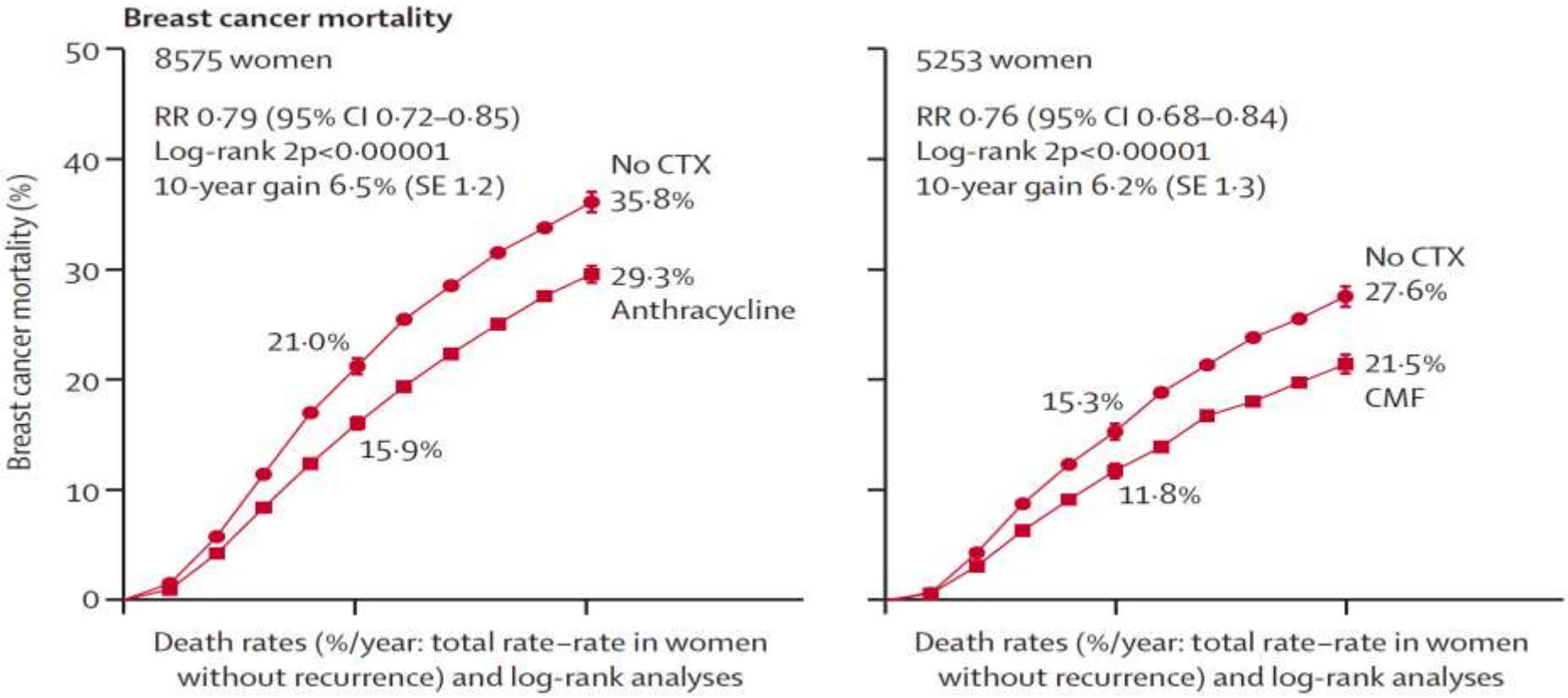

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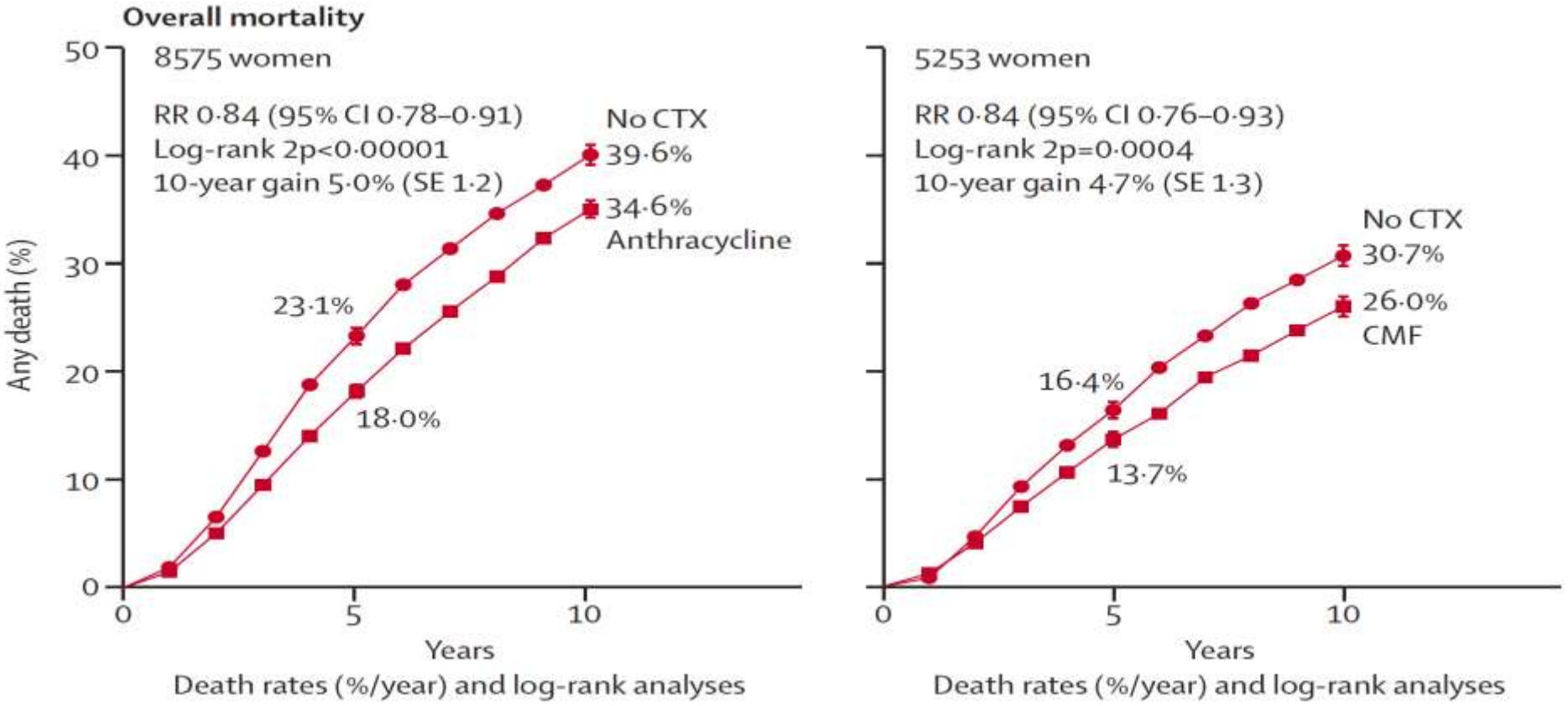

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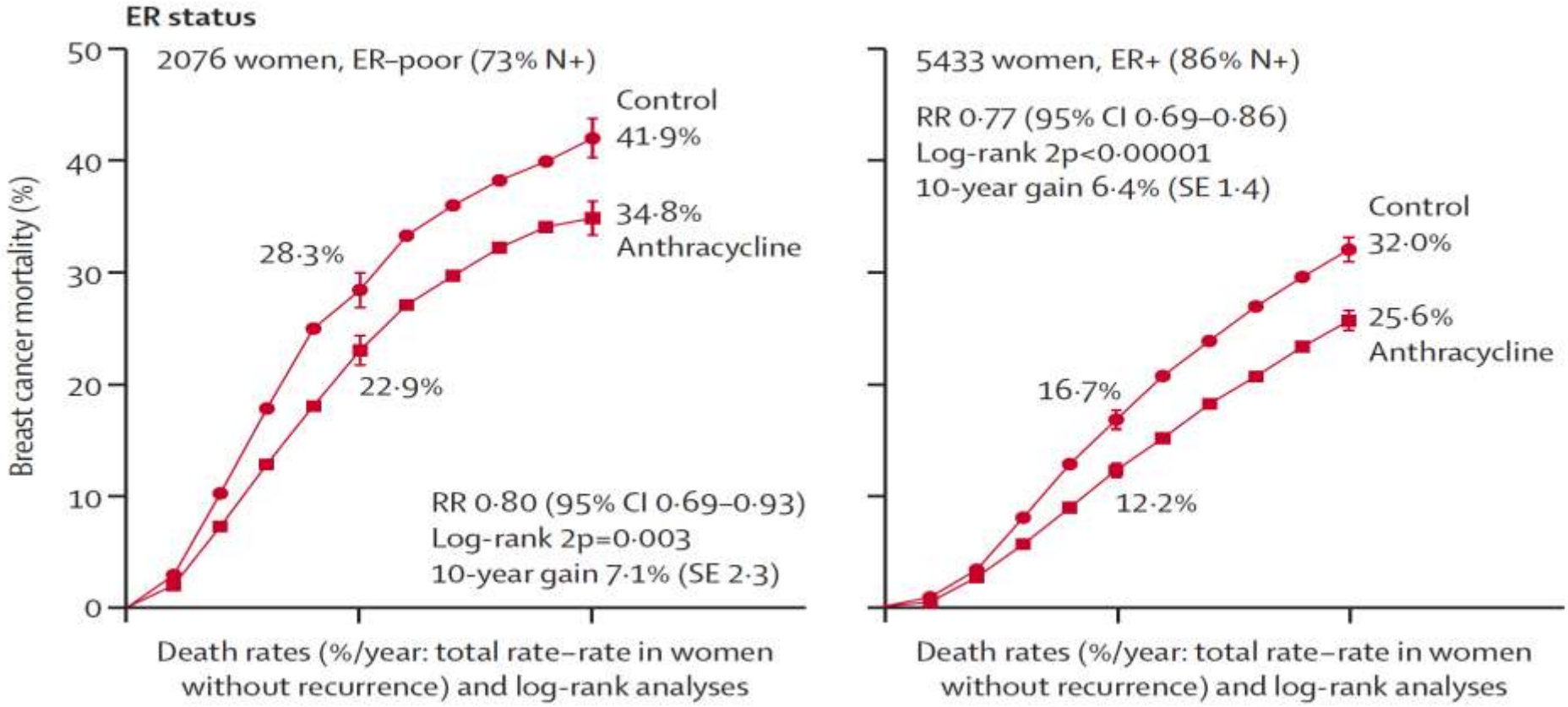

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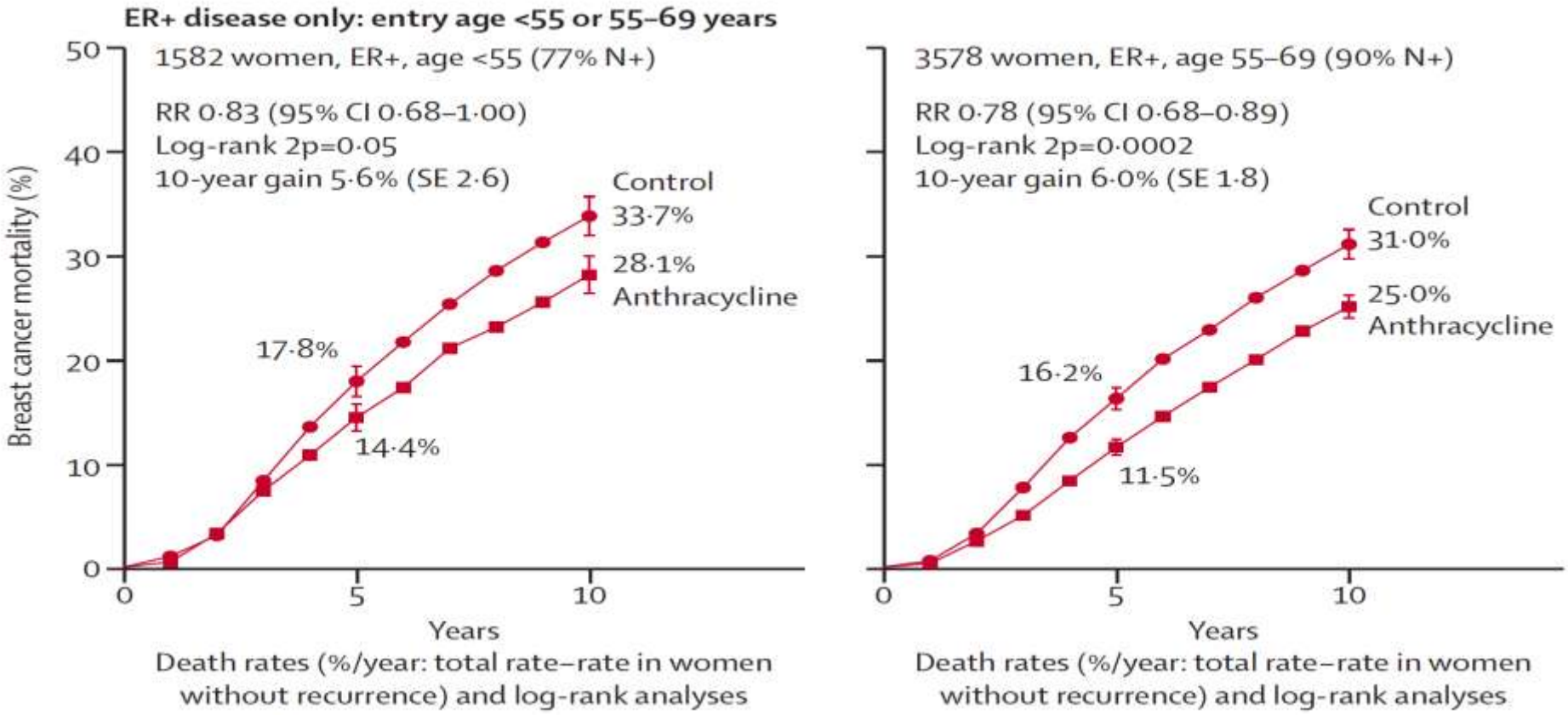
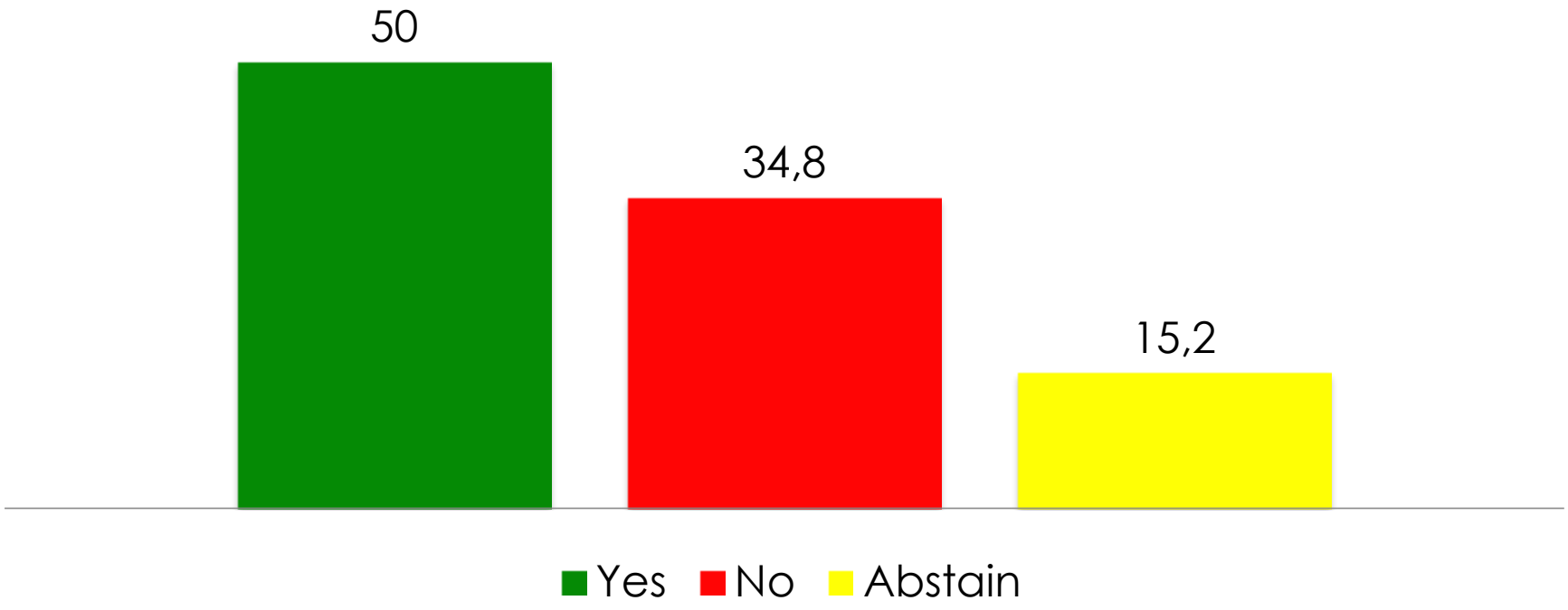


Lancet. 2012 February 4; 379(9814): 432–444

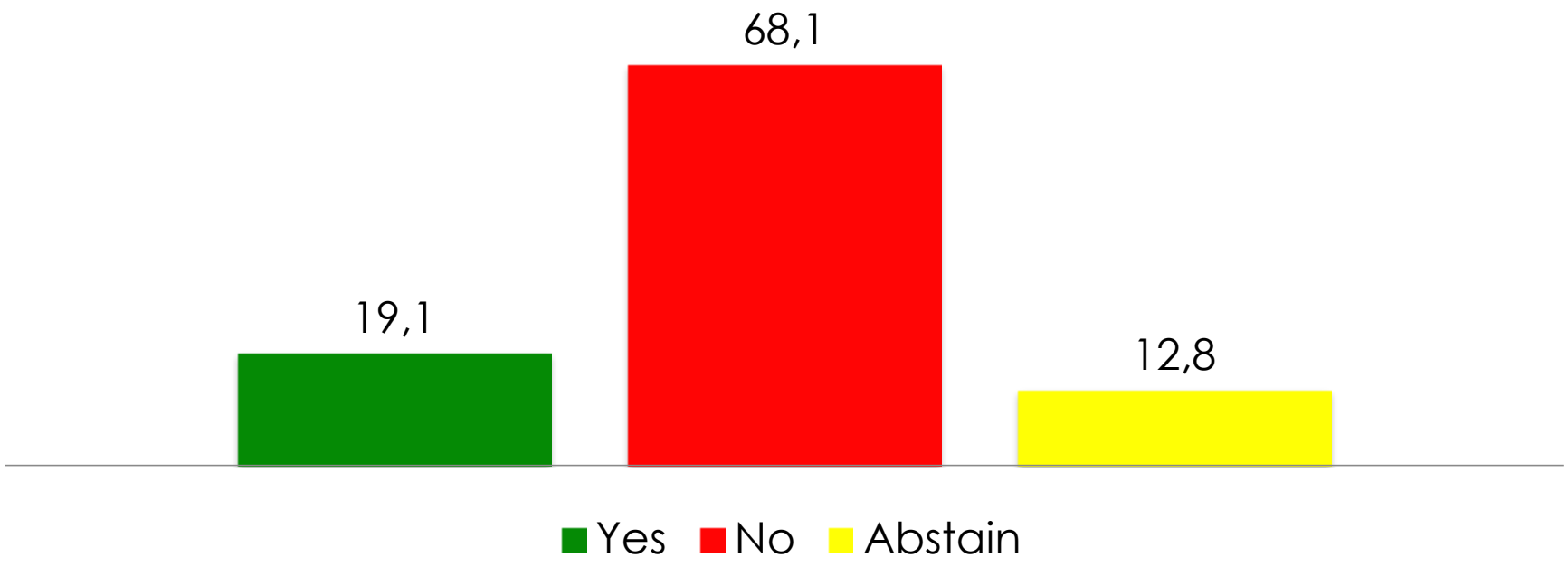
Chemotherapy
Luminal B HER2 (-)

Should CT extend for at least 6 courses?



Chemotherapy
Luminal B HER2 (-)

Should dose dense CT be preffered when CT indicated?

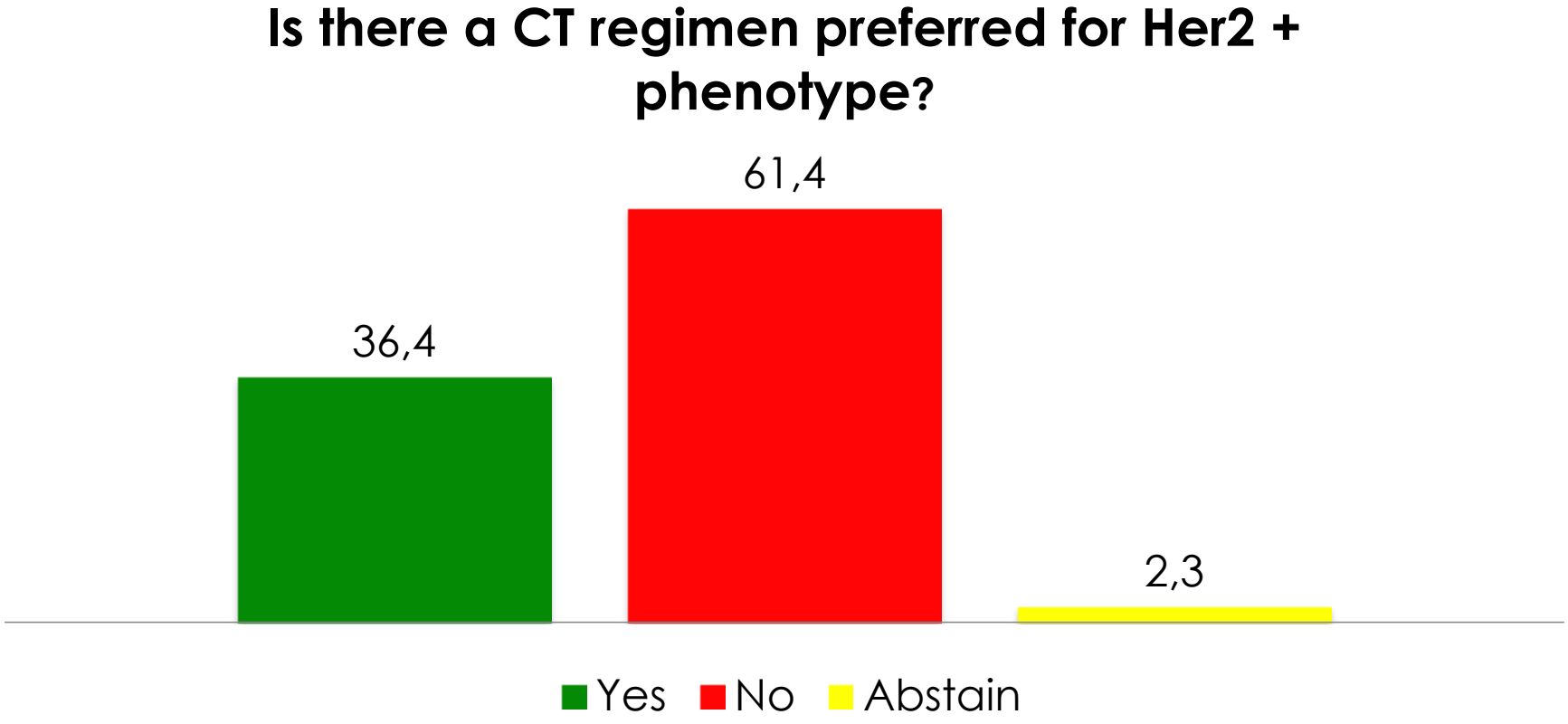


consensus

CHEMOTHERAPY
LUMINAL B HER2 (-)

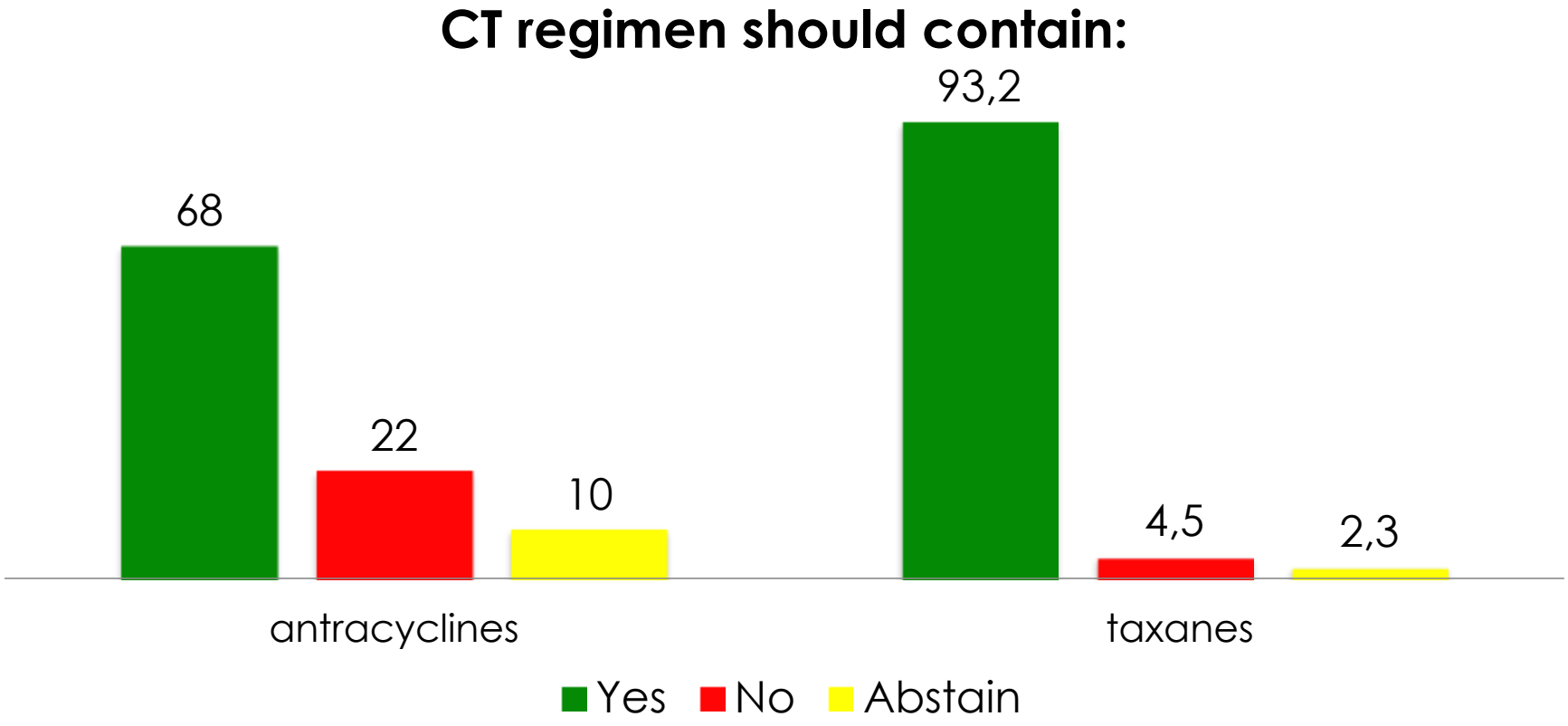
- Luminal B subtype by itself is sufficient to prescribe CT
- Ki67 is useful in defining luminal B subtype
- If Ki67 is used, higher than %20 should be used as thresold for defining luminal B subtype
- If given, CT regimen should contain antracycline and taxane rather than CMF
- CT should extend for at least 6 courses

Chemotherapy
Luminal B HER2 (+)



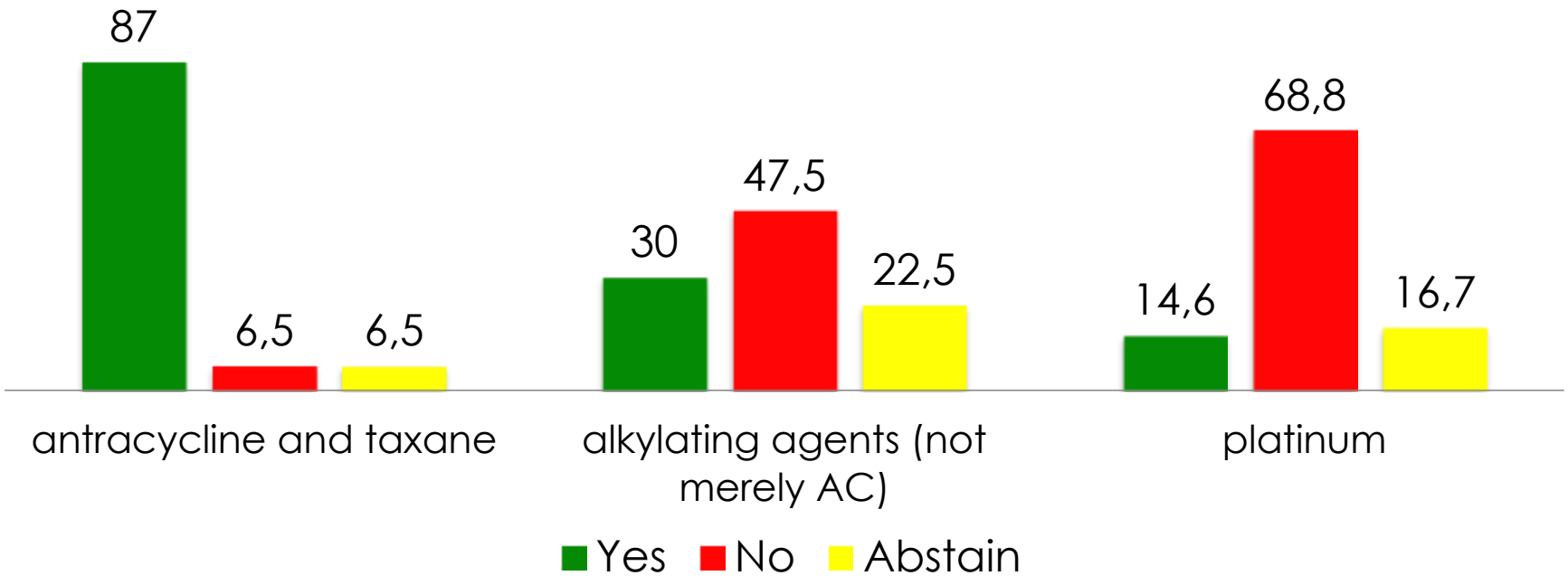
Chemotherapy

HER2 (+)



Chemotherapy
BASAL-LIKE

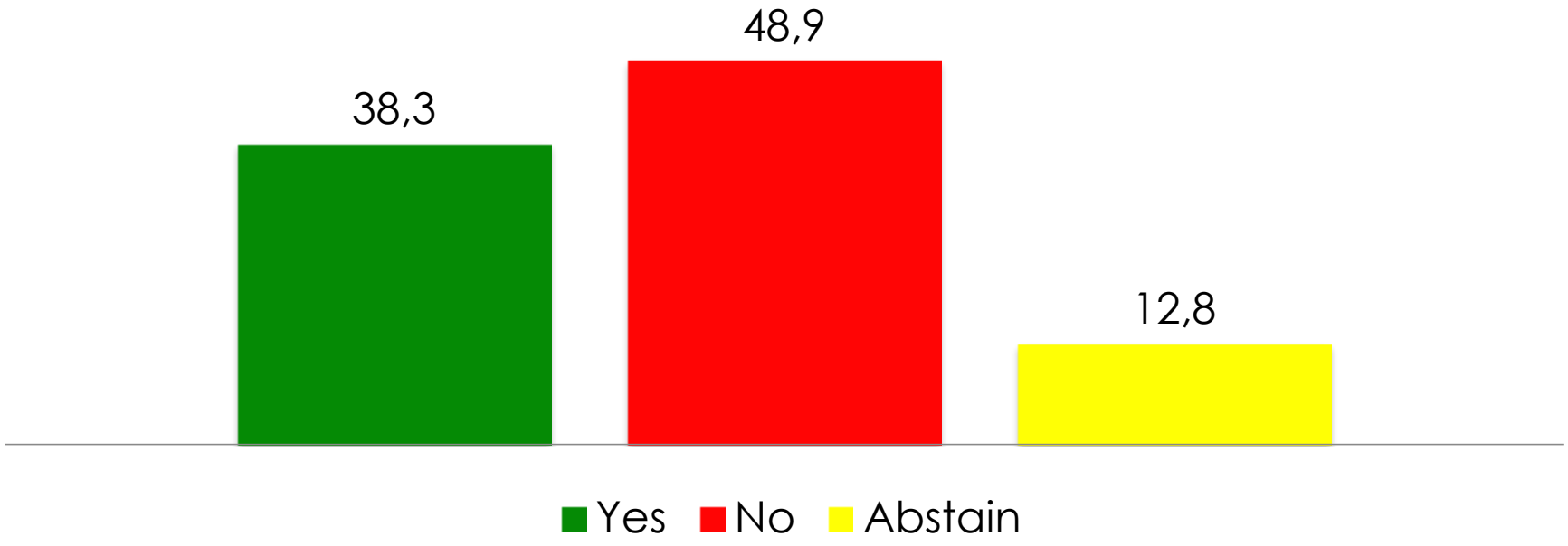
Should CT regimen for basal like (triple negative breast cancer – ductal) phenotype contains:



Chemotherapy

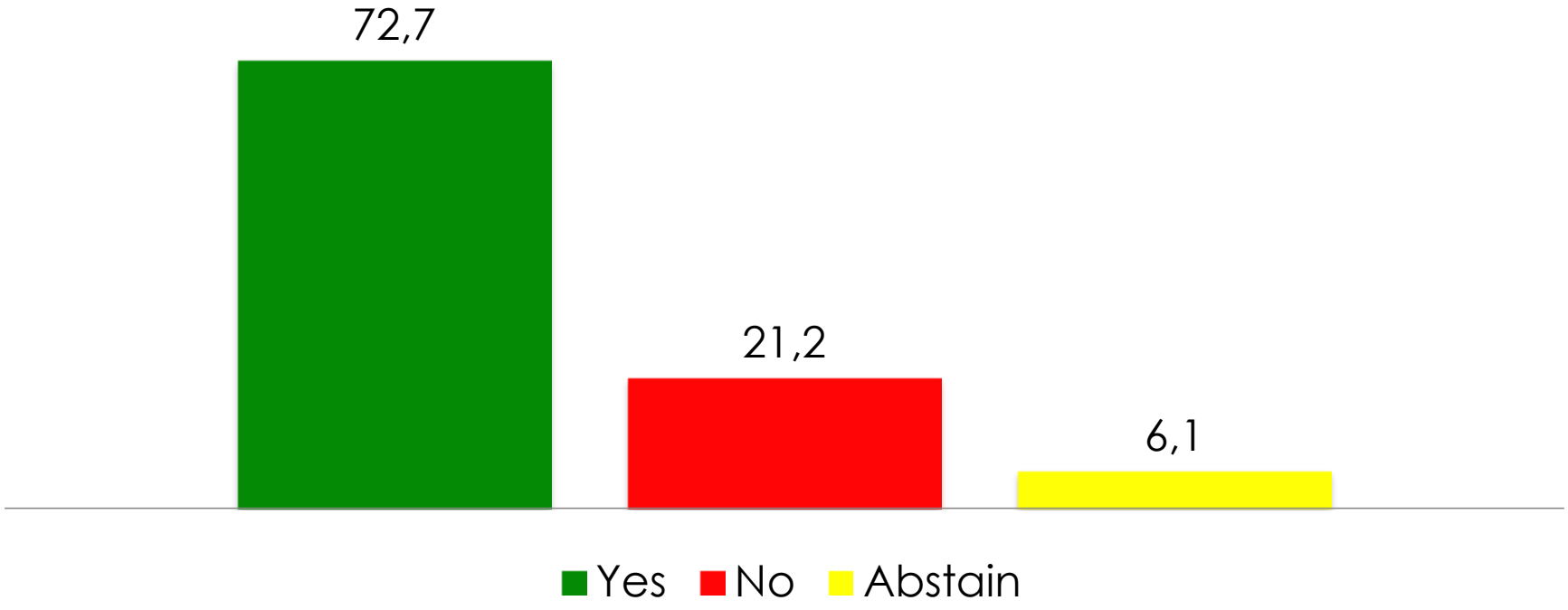
BASAL-LIKE

Should dose dense CT regimen with growth factor support be preferred?



Chemotherapy
Preference For Regimen

Are there reasons other than tumor characteristics to prefer specific CT regimens?



Chemotherapy
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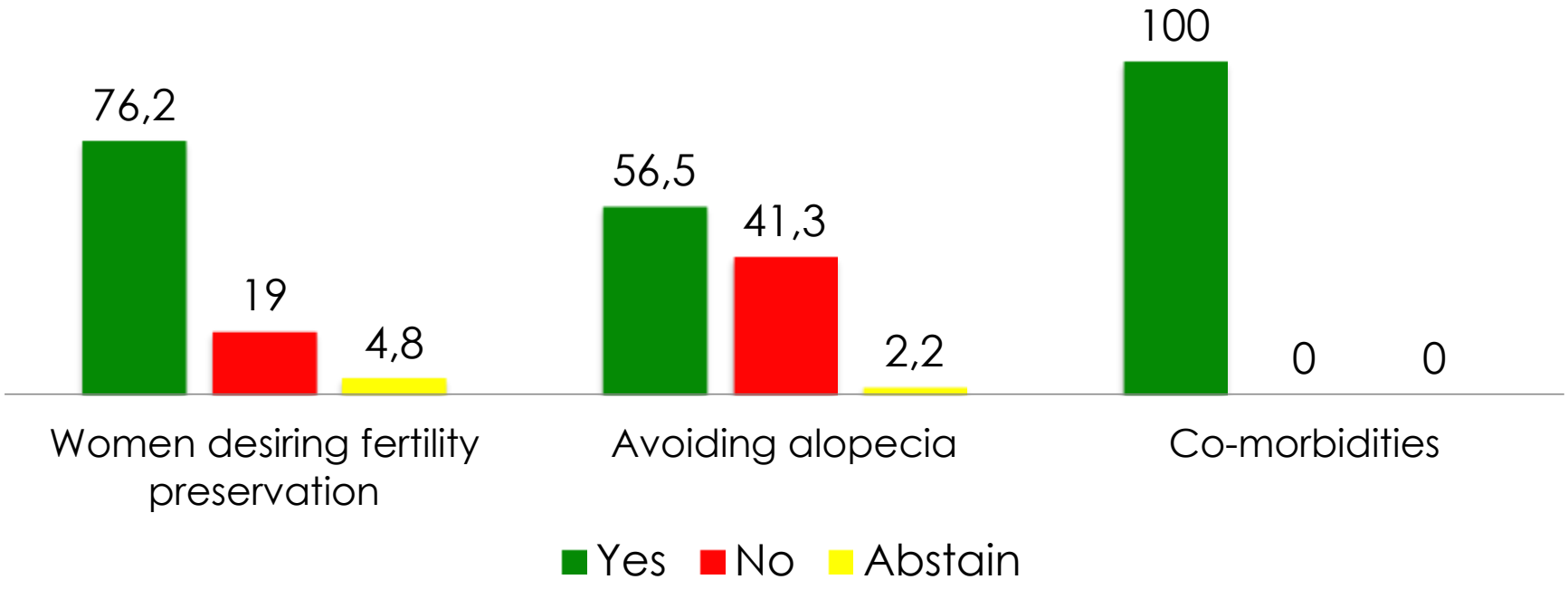
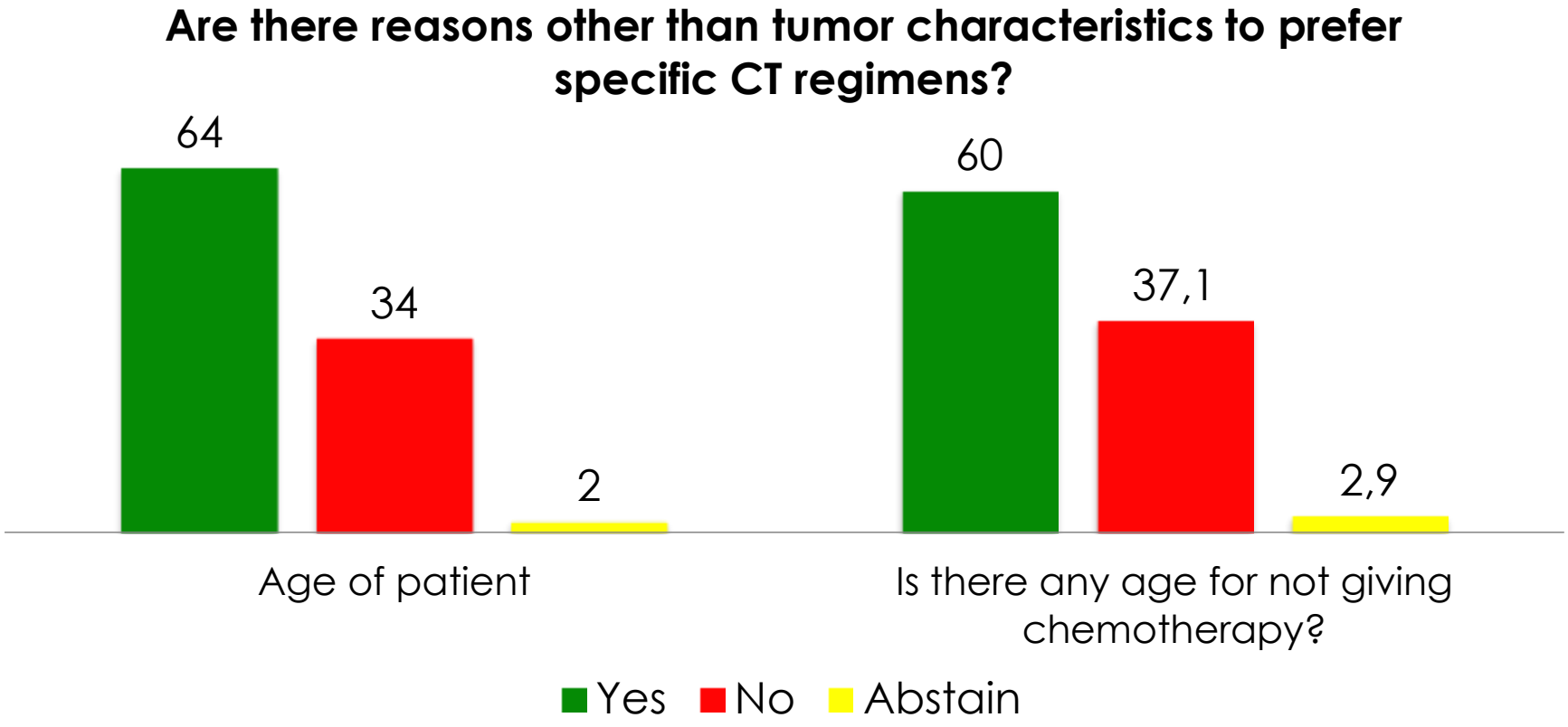


Chemotherapy
Preference For Regimen



Chemotherapy
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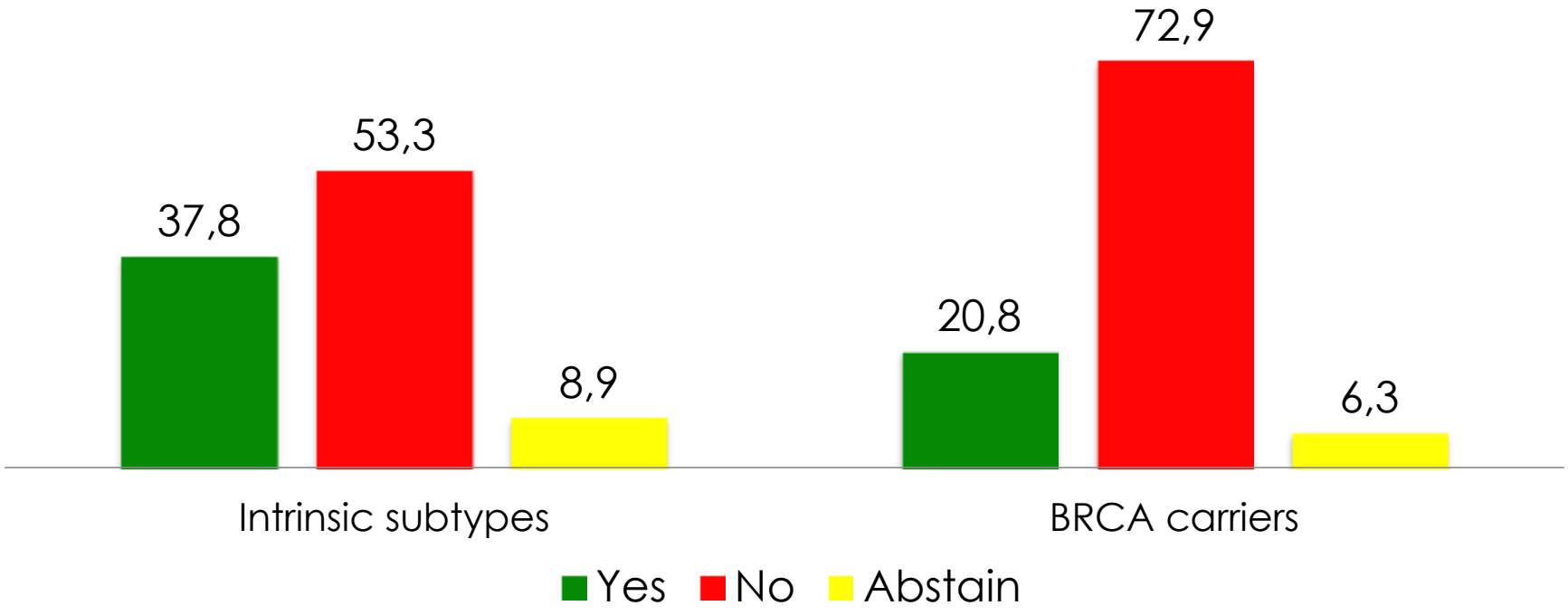
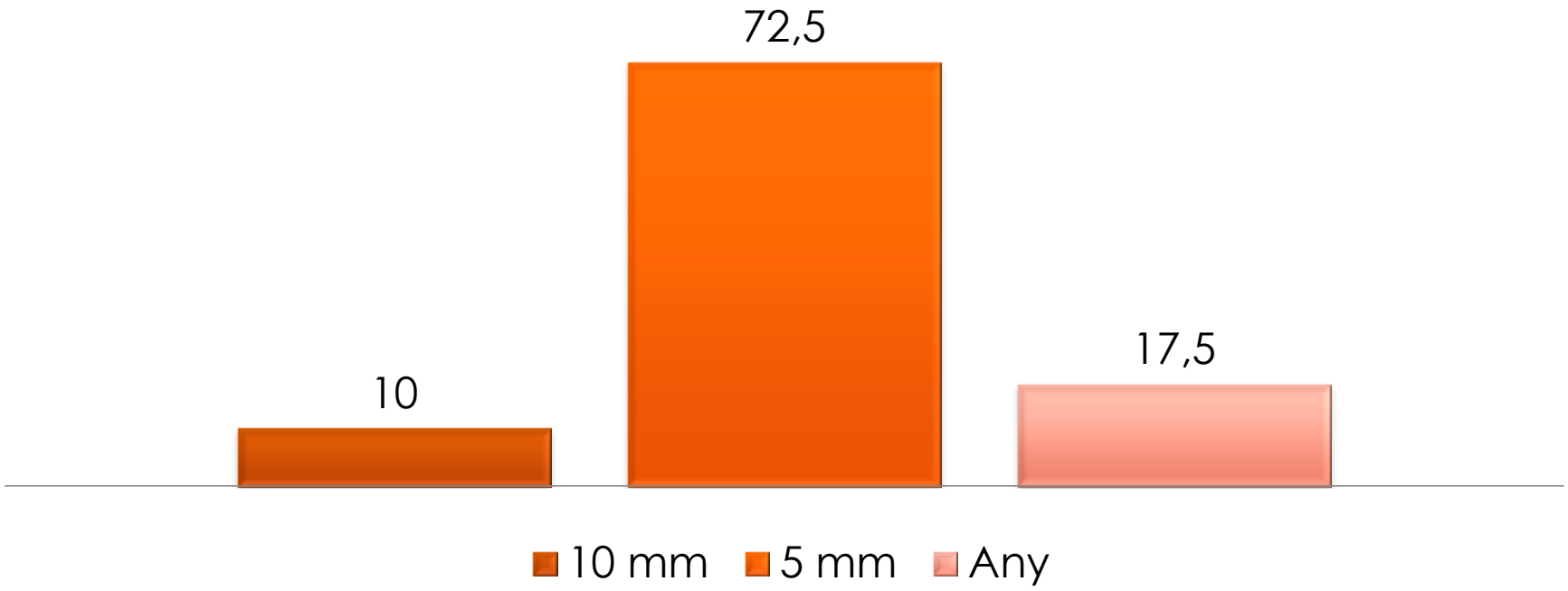
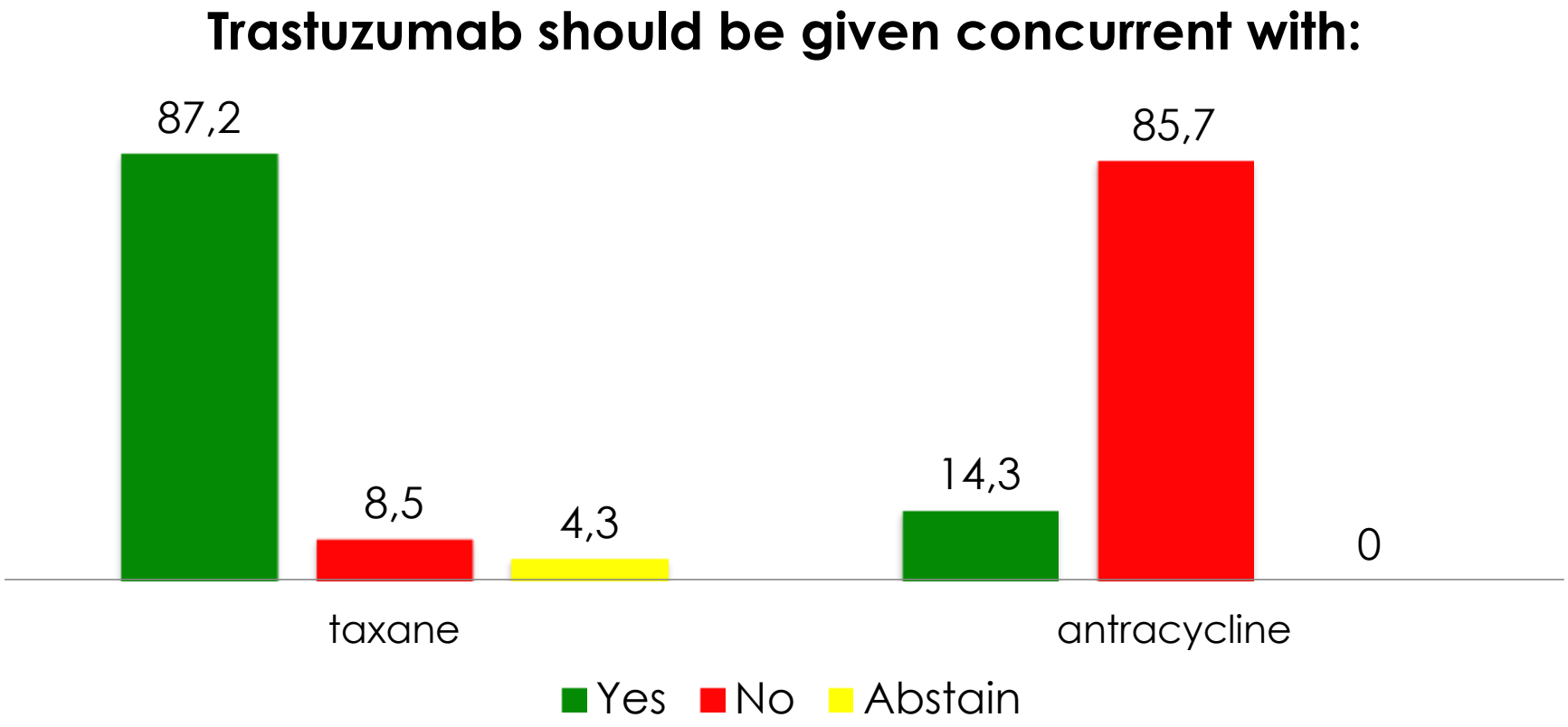


Anti HER-2 Therapy

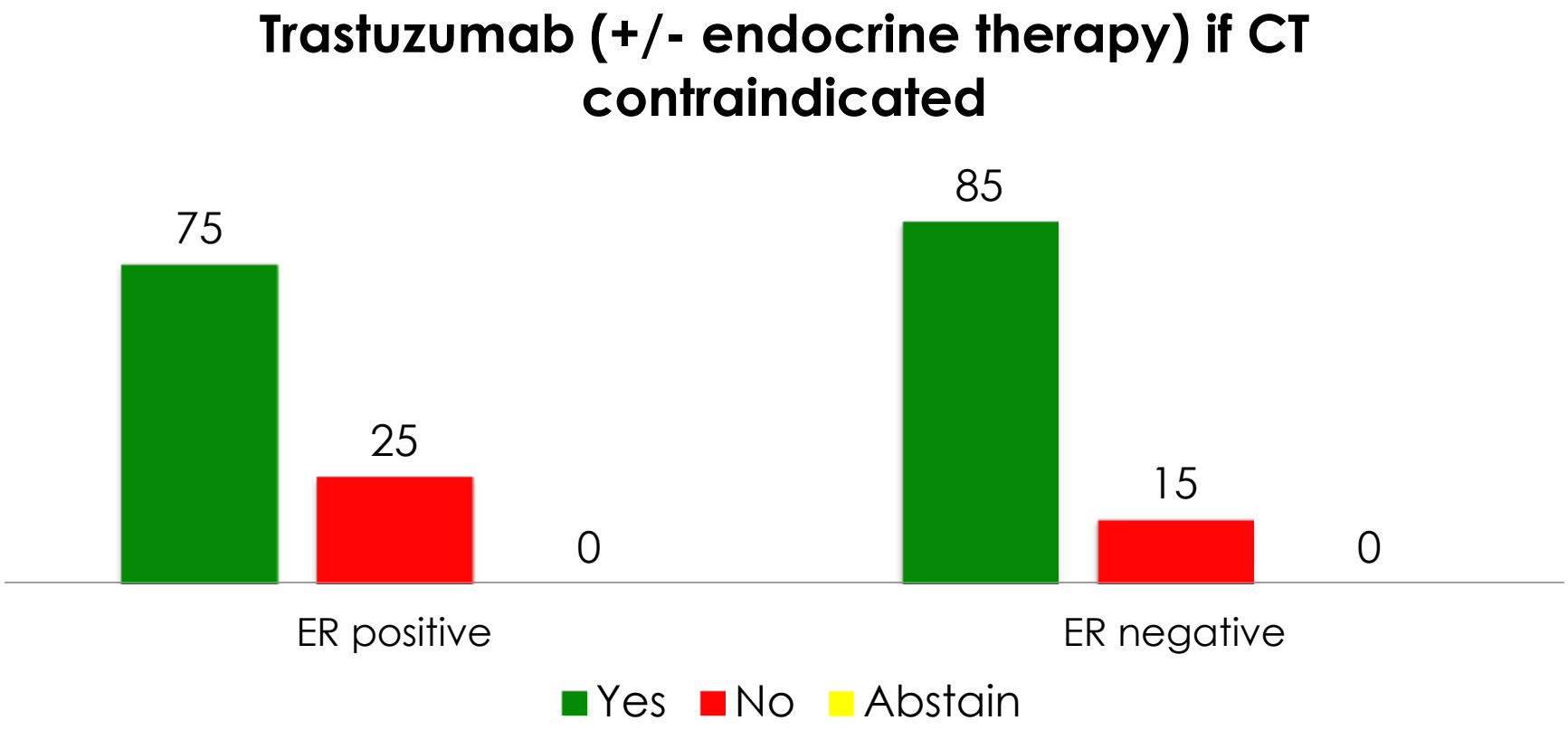
Minimum T size (invazive diameter) requring trastuzumab:



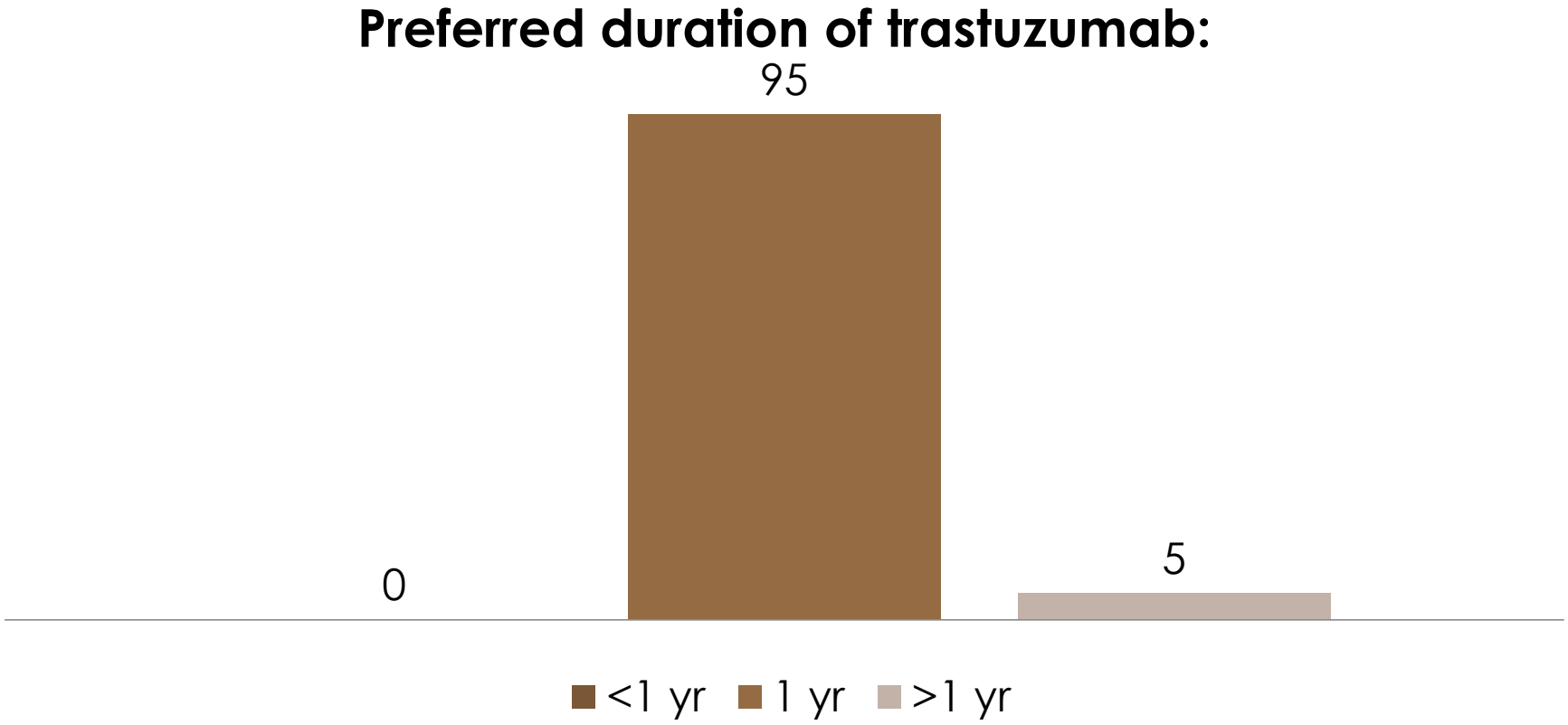
Anti HER-2 Therapy



Anti HER-2 Therapy

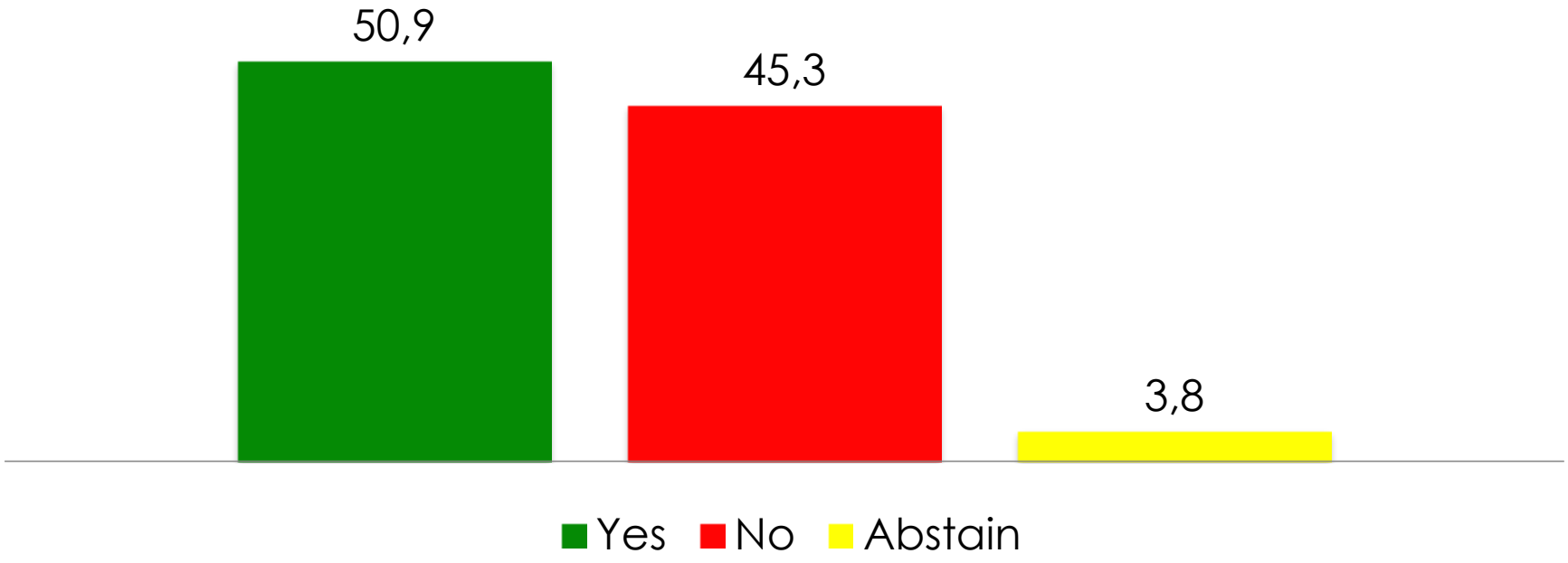


Anti HER-2 Therapy



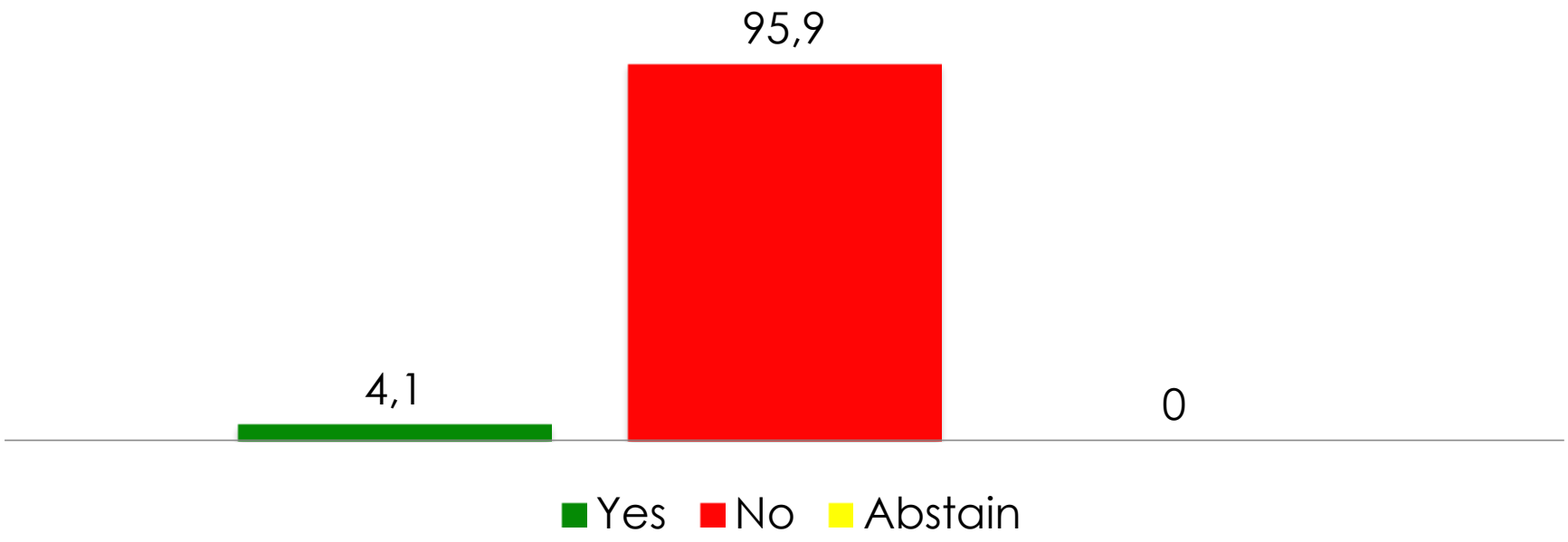
Neoadjuvant Systemic Therapy

Should the only aims of neoadjuvant CT be to facilitate subsequent local therapies?



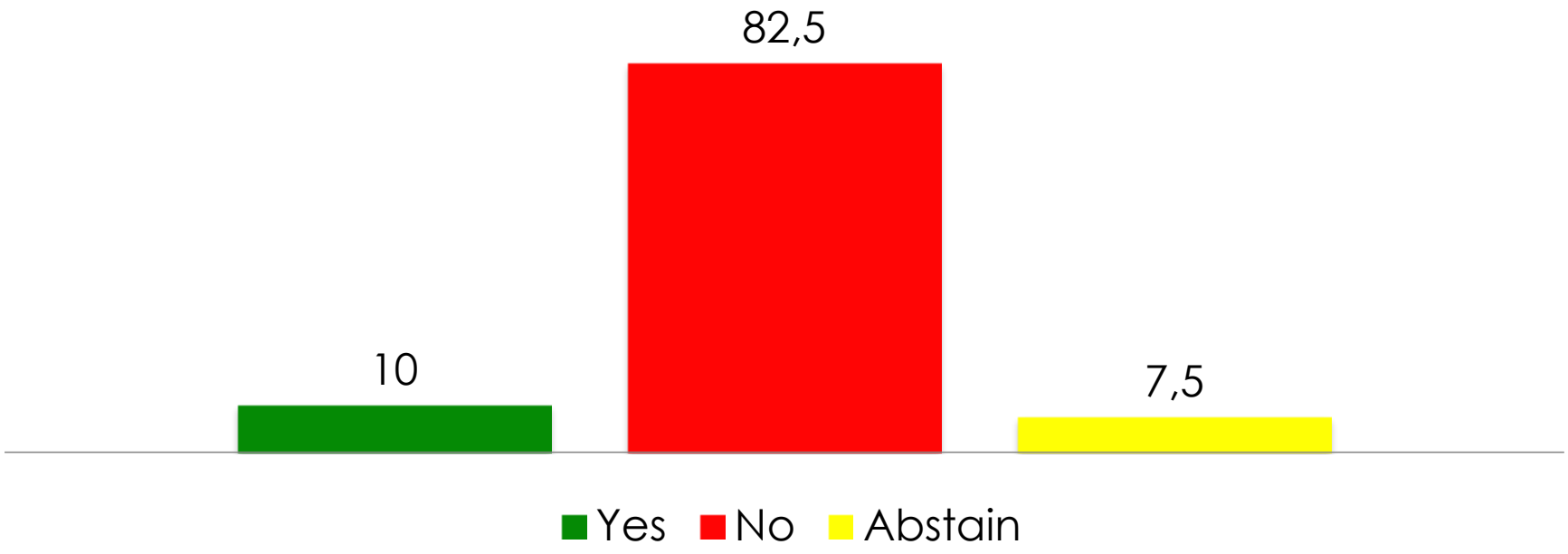
Neoadjuvant Systemic Therapy

After pCR to neoadjuvant CT subsequent adjuvant CT should be given?



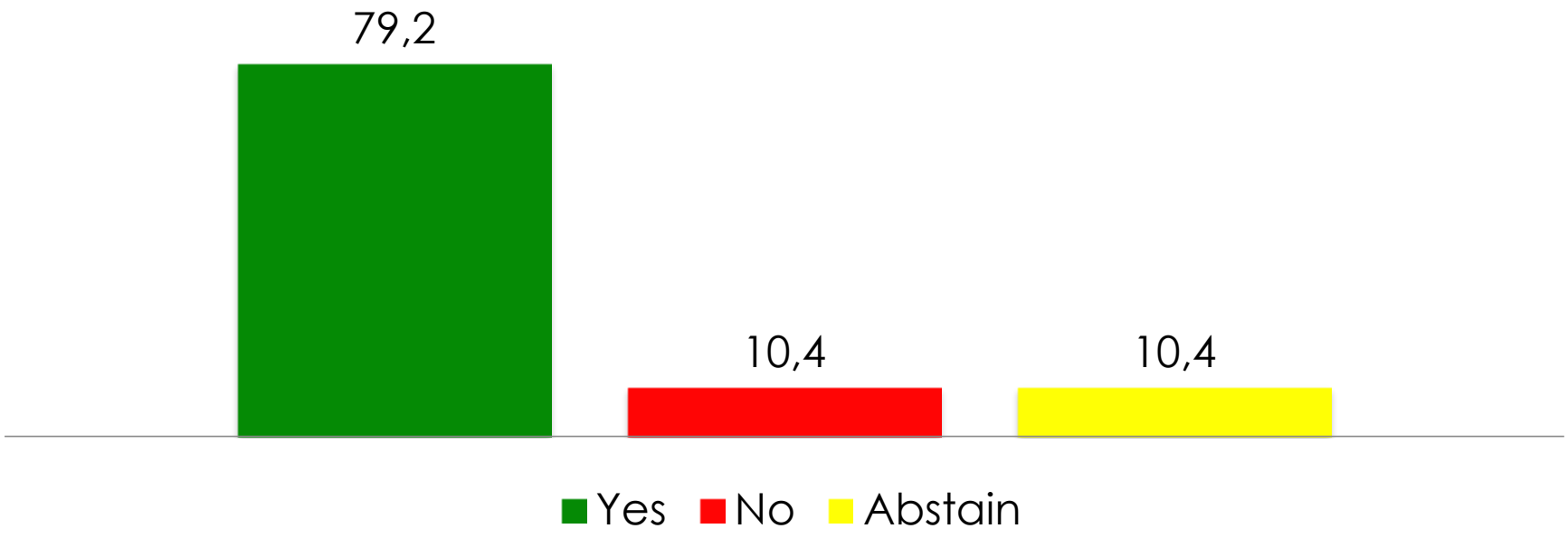
Neoadjuvant Systemic Therapy

After failure to achieve pCR with neoadjuvant CT, subsequent adjuvant CT should be given?



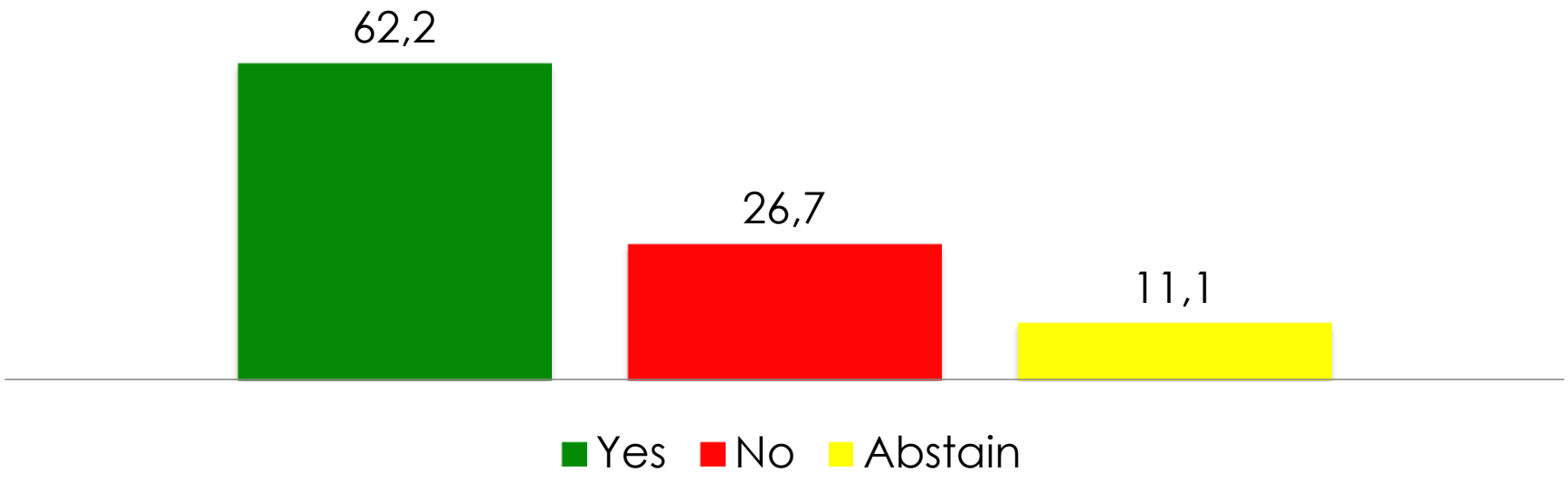
Neoadjuvant Systemic Therapy

If you are given neoadjuvant CT it is preferred to give entire CT upfront



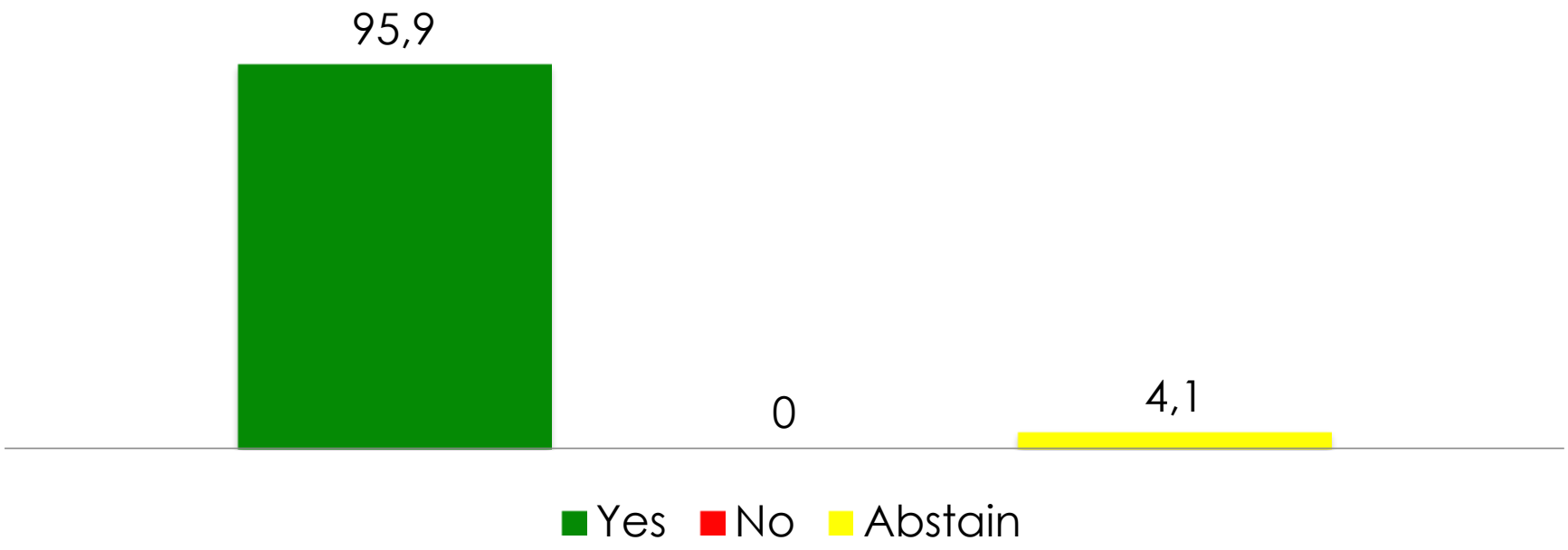
Neoadjuvant Systemic Therapy

If you have given a less than complete course of chemotherapy and the patient has a pCR, is additional chemotherapy warranted?



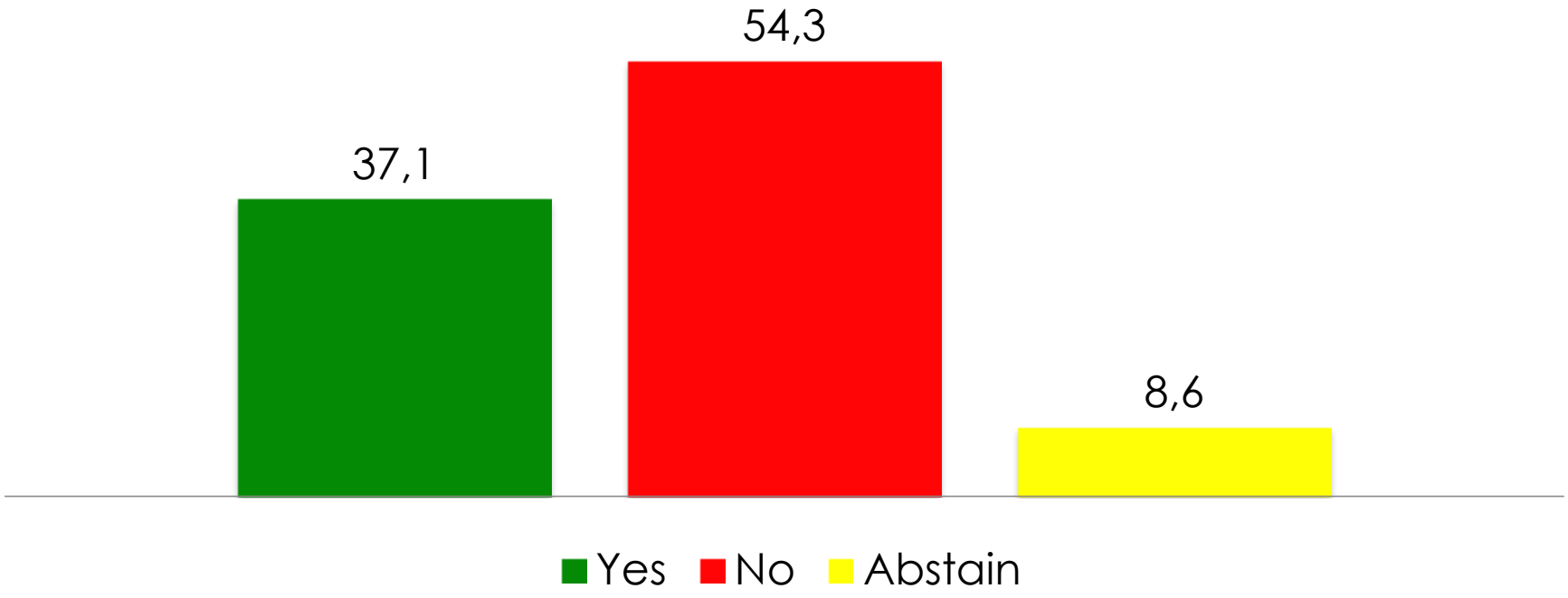
Neoadjuvant Systemic Therapy
HER2 Positive Disease

Should neoadjuvant systemic therapy contain anti Her2 drugs?



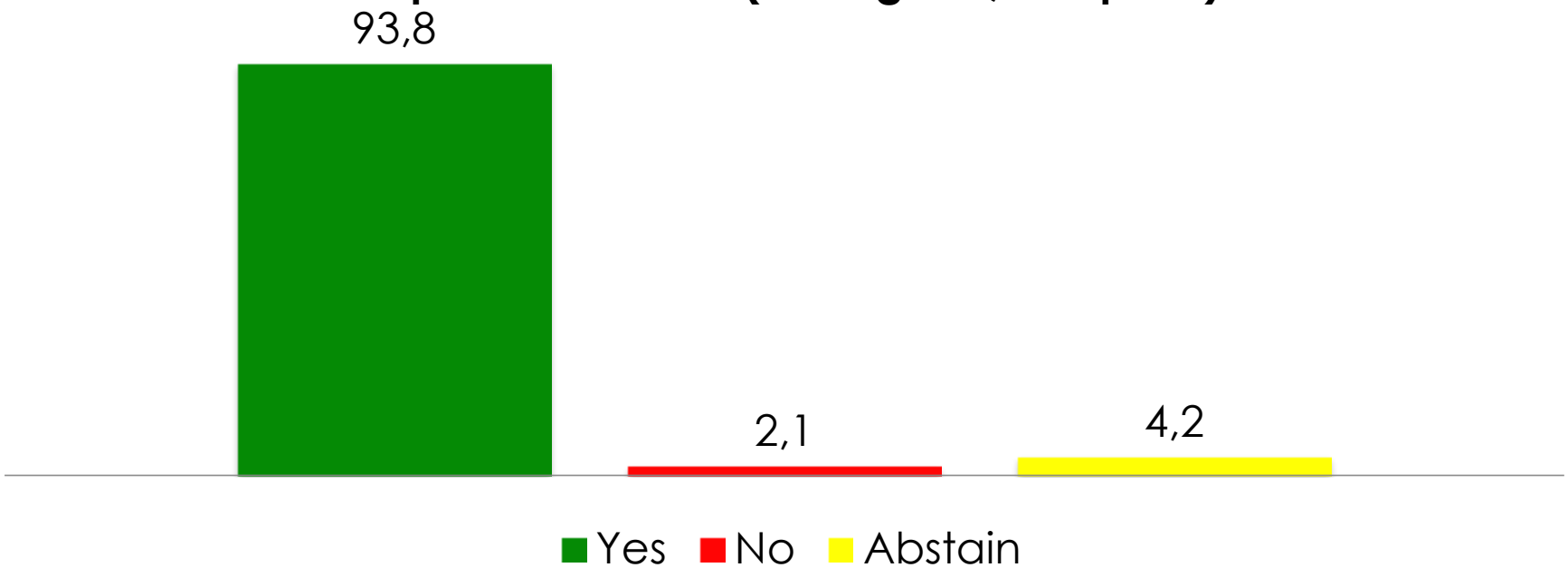
Neoadjuvant Systemic Therapy
HER2 Positive Disease

Should dual HER2-targeting be recommended in the preoperative setting for Her2-positive disease?



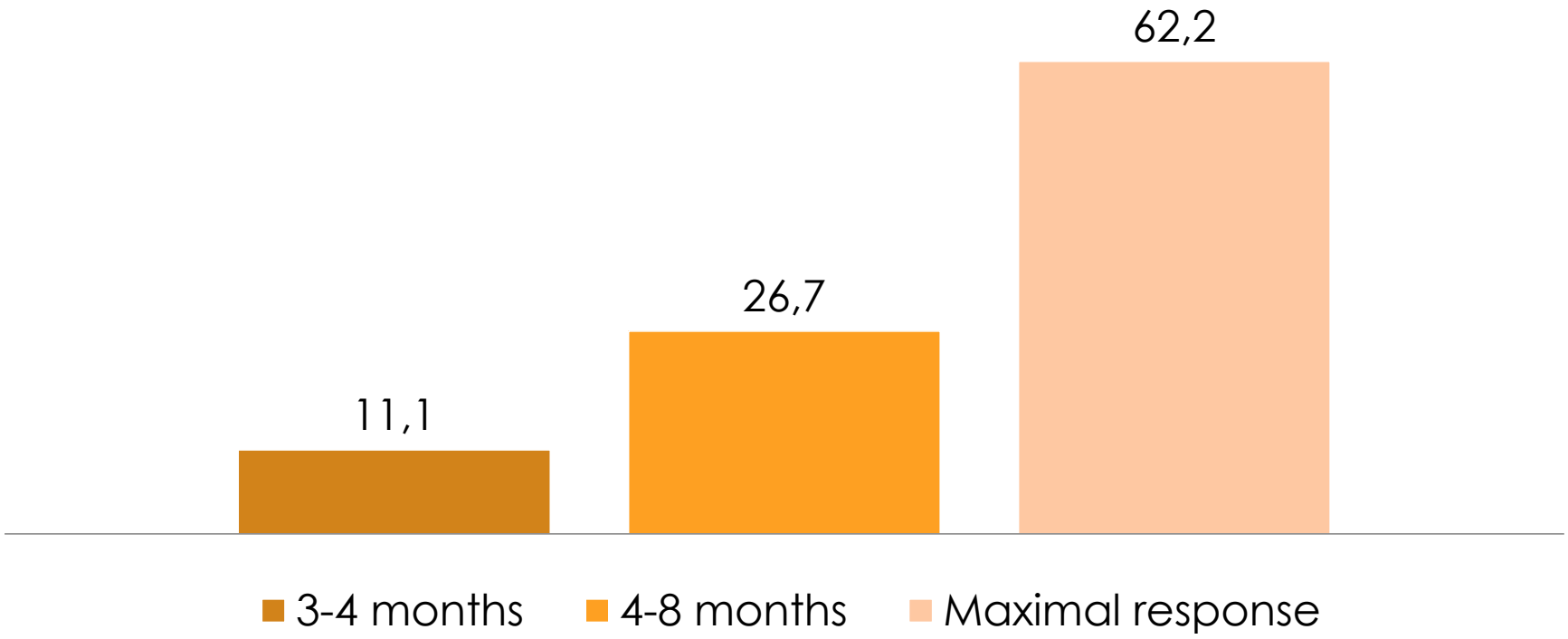
Neoadjuvant Systemic Therapy
Endocrine Therapy

Is neoadjuvant endocrine therapy alone a reasonable option for postmenopausal patients with high endocrine responsive tumor? (i.e. High ER, low prolif)



Neoadjuvant Systemic Therapy
Endocrine Therapy

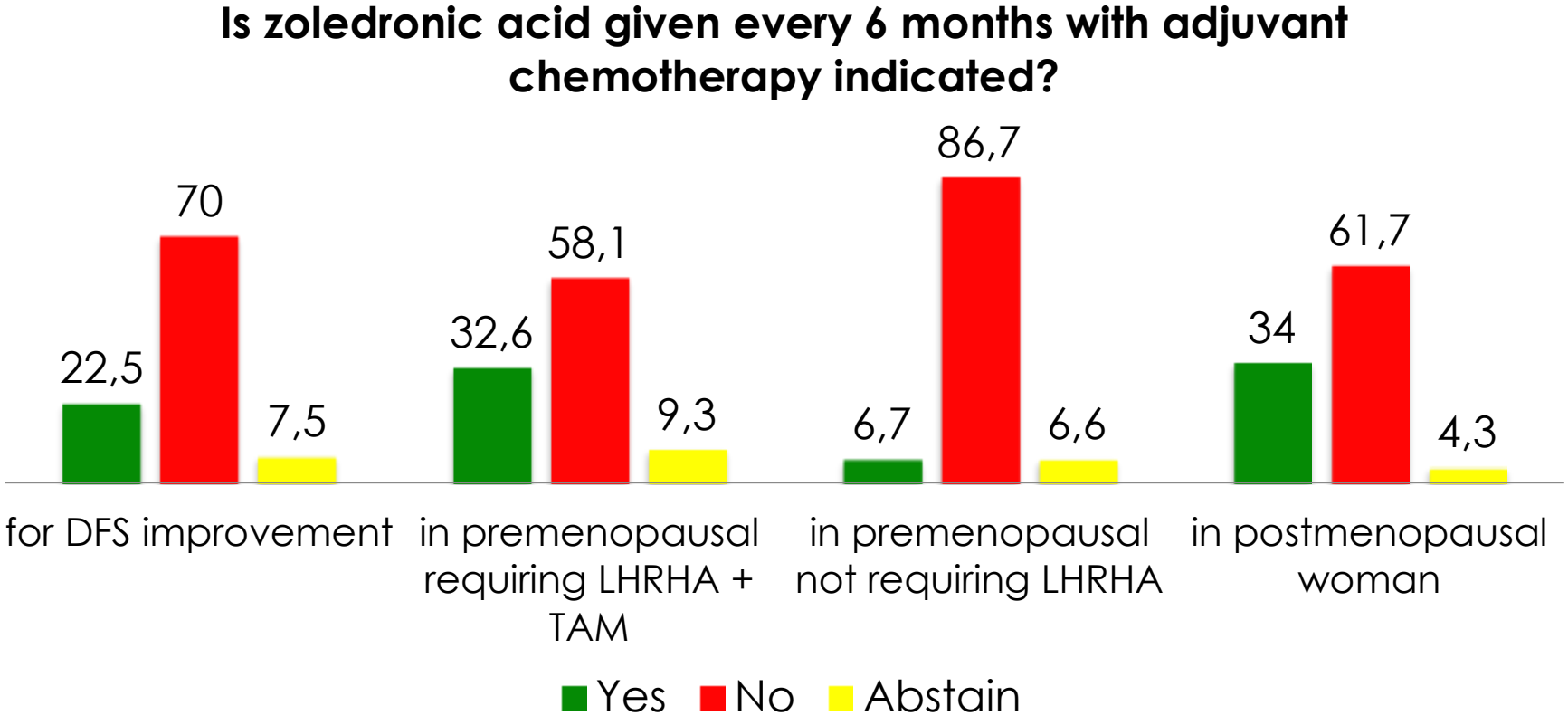
In which duration?



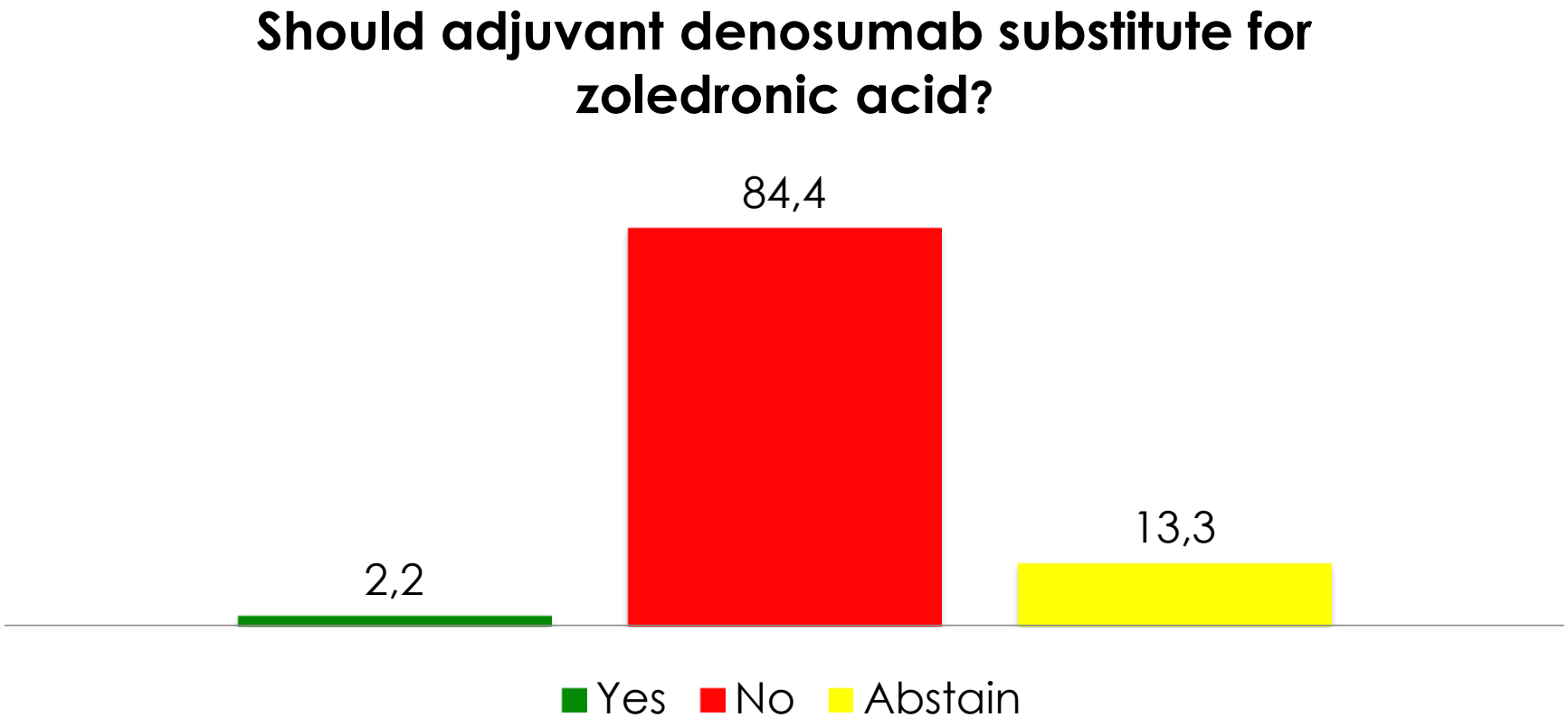
Conference Topic

Bisphosphonates

Bisphosphonates



Bisphosphonates

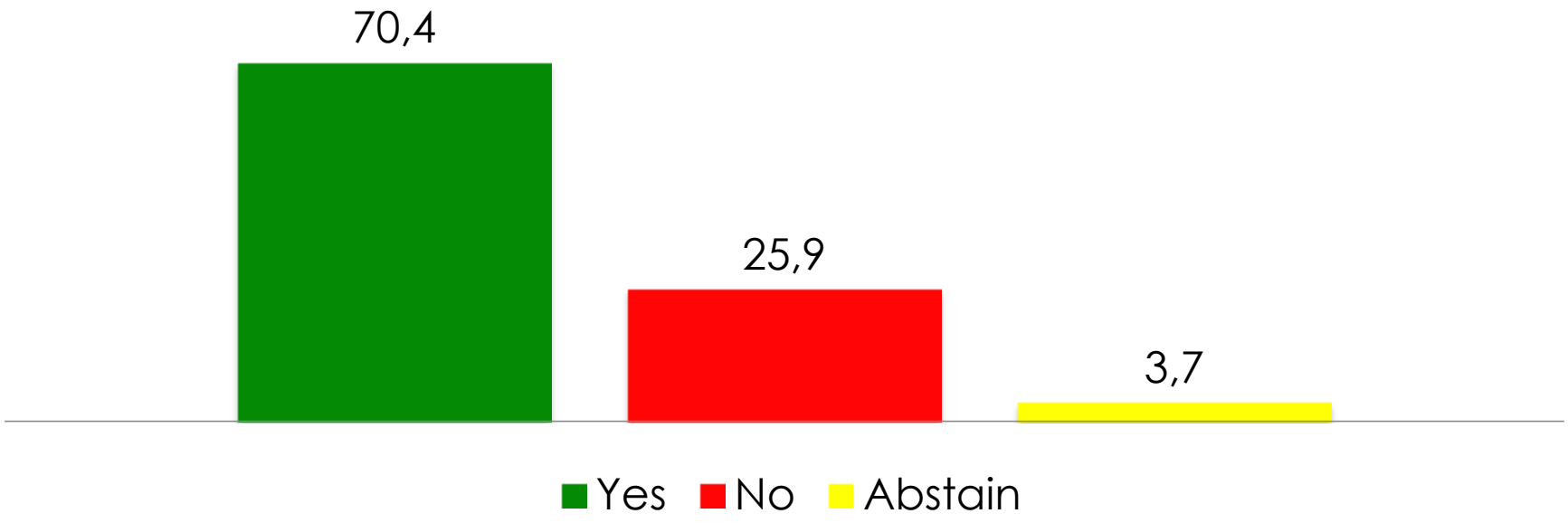


Conference Topic

Follow-up

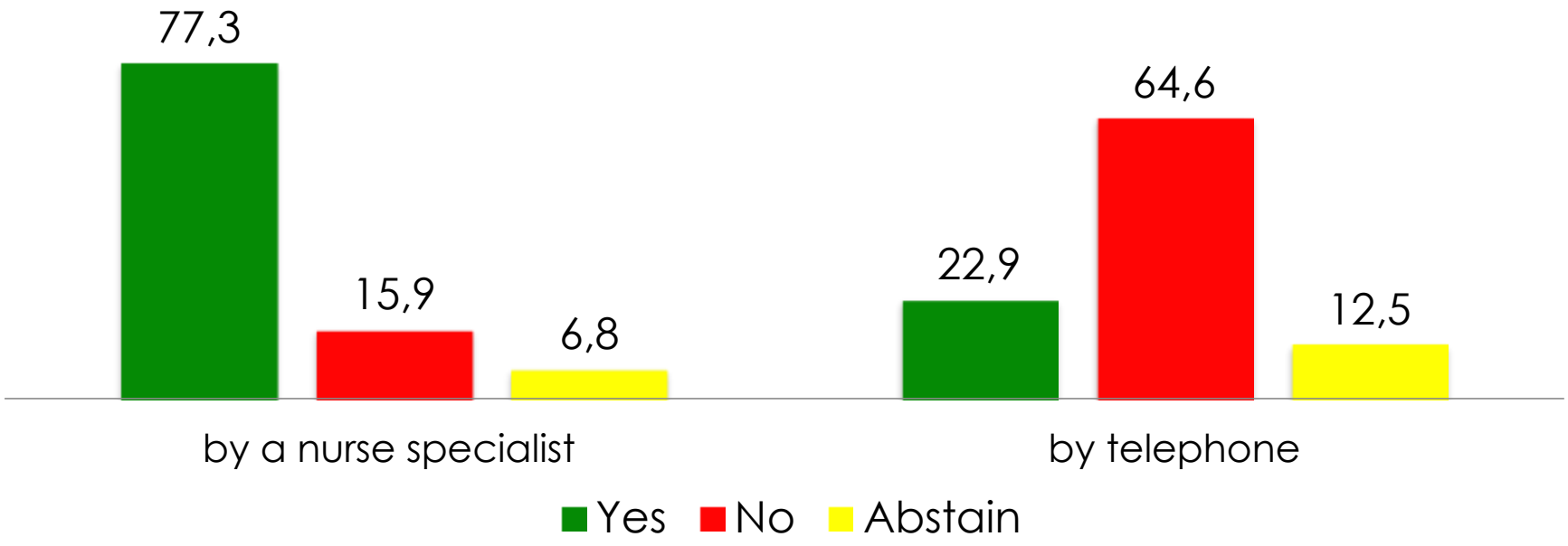
Follow-up
After Early Breast Cancer

Should all patients have regular follow-up with their surgeon/oncologist (excluding long term endocrin therapy)?



Follow-up
After Early Breast Cancer

Is regular follow-up by a nurse specialist or by telephone is an acceptible follow-up?



Follow-up
After Early Breast Cancer

Should patients have any form of routine imaging apart from mammography as part of their follow-up?