Radiotherapie

Less is more

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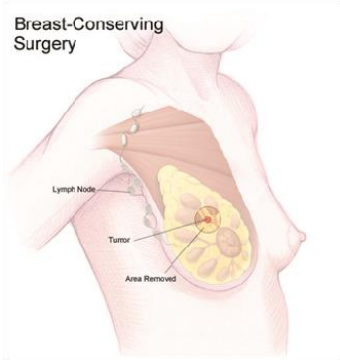
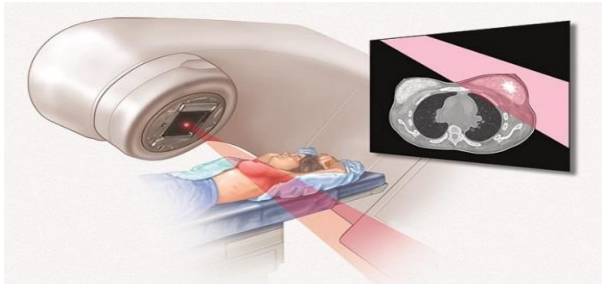
Introduction





+/- regional lymph nodes

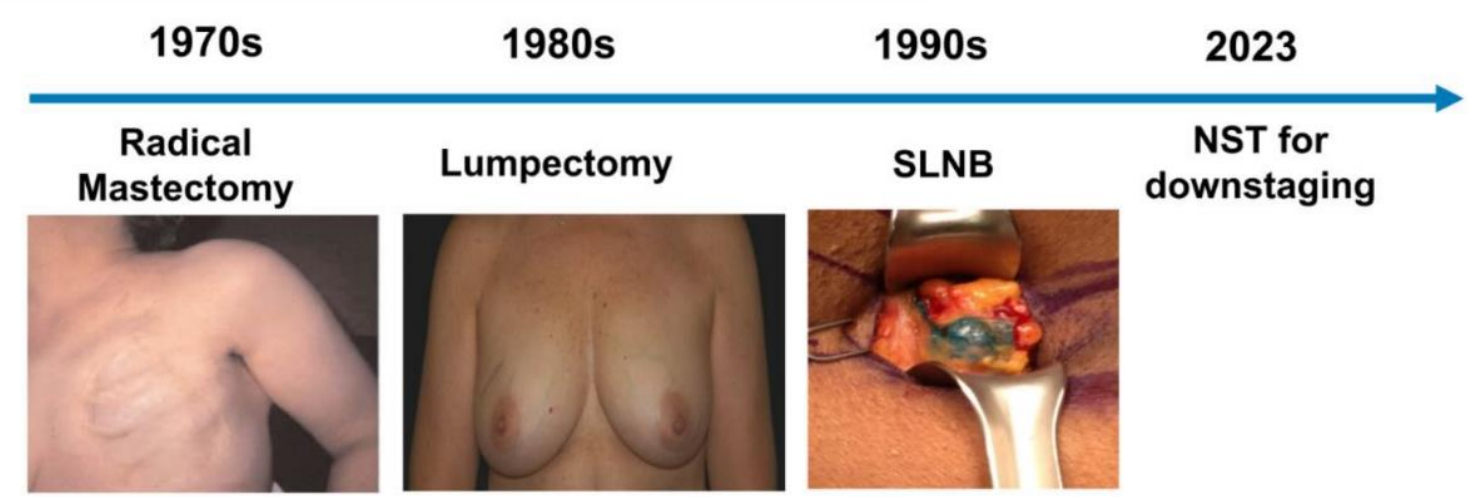
Better Local controle with factor 3 tot 4

Better Local / Regional Controle results in better DFS en OS na 10- 15 J

Introduction

➢ Trends in locoregional treatment

De-escalation



Introduction

21st century: it's all about…..

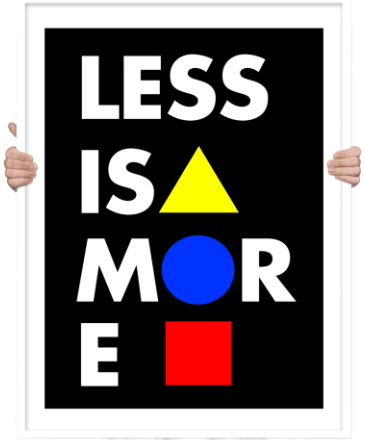
More survivors

late toxicity

cosmetic outcome

patient convenience

- Towards less fractions
- Towards less (smaller) target volumes
- RT omission



Less fractions

FAST Forward

RCT comparing 40/15 fx with 26 Gy or 27 Gy in 5 fx in early-stage BC

4096 pt – pT1-3 / pN0-1

- Primary endpoint: IBTR
- 10 Y update (ESTRO 2025)

	10 Y IBTR	5 j NTC
40 Gy / 15 fr / 3w	3.6%	9.9 %
27 Gy / 5 fr / 1w	3%	15.4 %
26 Gy / 5 fr / 1w	2%	11.9 %

FAST Forward

- Ultrahypofractionation (26 Gy in 1 week) is as effective and safe as standard 15 fraction-hypofractionation
- Higher normal tissue effect risk for 27 Gy in 1 week versus 40 Gy, but not for 26 Gy

26 Gy in 1 week = current standard of care for all RT indications without regional lymph nodes RT

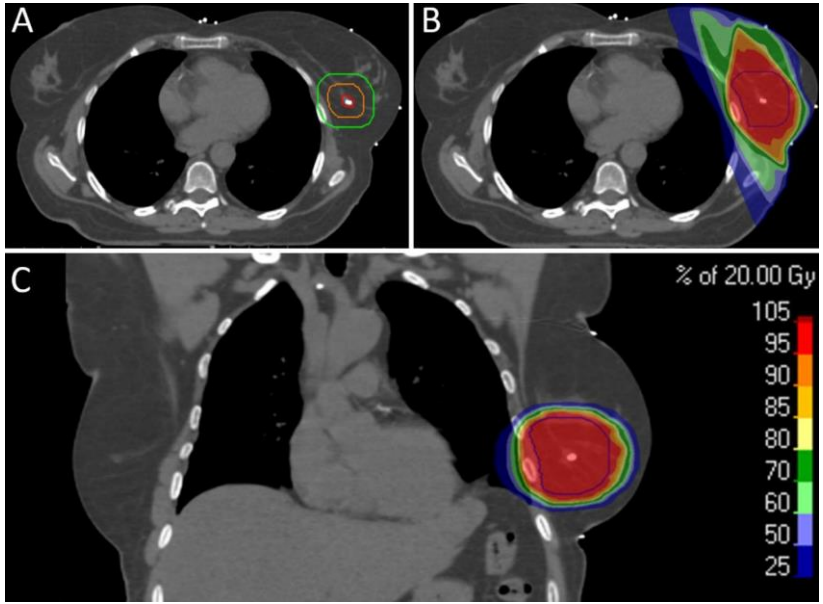
Less volume

Partial breast irradiation

- **Recurrence studies:**

  90% of local failures after BCT :

  - in **same** quadrant as original primary tumor
    - ➢ Area around tumour highest probability of in-breast recurrence



Partial breast irradiation sufficient in **low risk patients**?

- ➢ Might maintain high rate of local tumor control?
- ➢ Might reduce side-effects?

Sanders et al. 2007

Partial breast irradiation

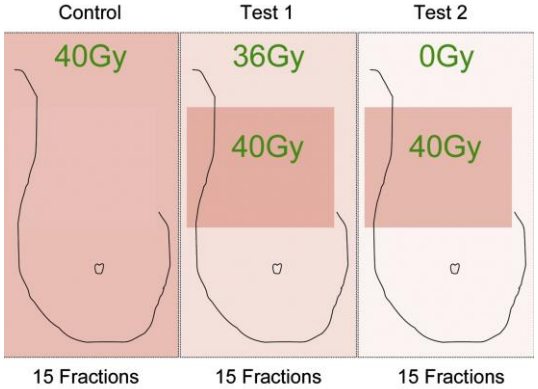
RCT	FU (years)	LR (%)			
		WBI	PBI	Toxicity	Cosmesis
NIO	17	7.9	9.6	=	PBI>WBI
IMPORT LOW	10	2.8	2.8	Acute/Late toxicity better with PBI	=
GEC-ESTRO	10.4	1.6	3.5	Late skin reaction better with PBI	=
Florence	10.7	2.5	3.7	Acute/Late toxicity better with PBI	PBI>WBI
RAPID	8	2.8	3.0	Acute toxicity better with PBI *Late toxicity reduction with WBI*	*WBI>PBI*
NSABP-B39	10.2	3.9	4.6	=	=
BARCELONA	5	0	0	Acute skin reaction better with PBI	=

Partial breast irradiation

Import Low Trial

2016 pt

674 WBRT
673 SIB
669 PBI



	5 y LR	10 Y
WBRT	0,5%	2,8 %
SIB	0,73 %	1,9 %
PBI	1,1 %	2,8 %

Non inferiority
Equivalent or less NT adverse effect

Florence trial

520 pt

260 WBRT
520 APBI

R

PBI
30Gy/5#/1w

WBRT
50Gy/25#/5w
+ boost 10Gy/5#

	10 Y IBTR	Tox 6 mnd
WBRT	2,5 %	28,8 % Gr1, 31,2% Gr2, 6,5% Gr3
PBI	3,7 %	19,1% Gr1, 2% Gr2, 0 % Gr3

Non inferiority
Treatment related toxiciteit / cosmesis outcome in favor APBI

Partial breast irradiation

- **RAPID trial (2019)**
  - 2135 patients: >40 year, unifocal < 3cm tumor, node negative

	8 Y IBRT	Induration / teleangiectasia 8 Y
WBRT 50 Gy / 25# - 42,5 Gy / 15#	2,8 %	13 % (Gr 2+)
APBI 38,5 Gy / 10” BID (5-8 d)	3 %	35 % (Gr 2+)

➢ **Worse cosmetic outcome (29 vs 17% of patients) and late toxicity**

Partial breast irradiation

Consideration	Suitable	Cautionary	Unsuitable
Age	≥50 years of age	40–49 years of age if meet all other "suitable" criteria or ≥50 years of age with one or more other cautionary feature	<40 years of age or 40–49 years of age and not meeting all other criteria
Genetics	BRCA 1/2 negative	–	BRCA 1/2 positive
Margins	≥2 mm	<2 mm	Positive
DCIS	≤2.5 cm, screen-detected, low-intermediate grade, margins ≥3 mm	≤3.0 cm not meeting criteria for "suitable"	>3.0 cm
Size	≤2.0 cm	2.0–3.0 cm	>3.0 cm
LVSI	None	Limited/focal	Extensive
Hormone-receptor status	ER positive	ER negative	–
Histology	Invasive ductal	Invasive lobular	–
Extensive intraductal component	None	≤3 cm	>3 cm
Focality	Clinically unifocal	–	Clinically multifocal or microscopically multifocal with total size >3.0 cm
Centricity	Unicentric	–	Multicentric
Nodal status	pN0	–	pN+
Neoadjuvant therapy	None	–	Any

DCIS, ductal carcinoma in situ; LVSI, lymphovascular space invasion; pN0, pathologically node-negative; ER, estrogen receptor; pN+, pathologically node-positive.

- **In well-selected patients similar local recurrence rates for (A)PBI compared to WBI**
- **(A)PBI similar and often better toxicity**

ASTRO Guidelines voor APBI

RT omission

De-escalation in post-menopausal women with low-risk ER+ breast cancer

RT omission?

- Most trials have looked at de-escalation of radiation therapy (RT)

		IBTR	
CALBG 9343 (>70j) 1994-99	636 pt T1cN0 HR+ RT + TAM vs TAM	5 Y: 4 % vs 1 %	No difference DM / OS
PRIME II (> 65 j) 2003-09	1326 pt T1T2 <3cm / HR+ RT vs no RT TAM aangewezen	10 Y : 9.5 % vs 0.9 %	No difference DM / OS

- Increased incidence of local recurrence BUT no detrimental effect on distant recurrence or OS as **long as adherent to ET**

Kunkler et al. 2023 N eng J Med

2020-2023: omit RT, go endocrine therapy!

RT omission?

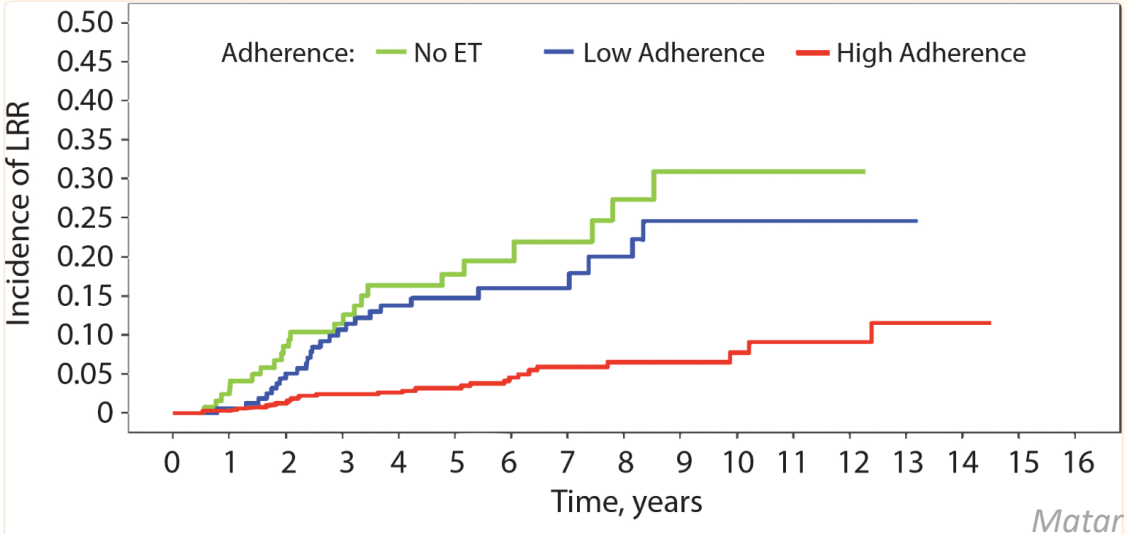
trial	Fase 3	N	Main selection criteria	Therapy	FU	Recurrence
Lumina	No	500	55+j, T1N0 G1-2, KI67 -	ET	5 Y	2,3 %
IDEA	No	200	50-69j, T1N0 Oncotype RS: -18	ET	57 mnt	4 %
Precision	No	690	50-75J, T1N0 G1/2 Pam 80 LuminalA	ET	27 mnt	0,3 %
Primeti me	No	1623	60+J, T1N0, G1-2, IHC4+C	ET	Closed 03/22	
Natural	Yes	926	60+J, T1N0 G1/2	ET vs ET + PBI	acruing	na
Expert	Yes	1170	50+J, T1N0 G1/2 Pam50 ROR60	ET vs ET + WBI	acruing	na
Debra	Yes	1670	50-70j T1N0 Oncotype RS: -18	ET vs ET + WBI	acruing	na
Europa	Yes	926	70+J, T1N0 G1/2 , Ki67 -20	ET vs RT		na

"Can Tumor Biology be incorporated into decisions on RT omission?"

- Newer trials using molecular markers to identify those suitable for RT omission
- Patients in these trials had **excellent ET adherence**

Meanwhile in real life…

- **Endocrine therapy adherence:**
  - > 30% discontinue ET ! (range 53-86%)
  - Adherence decreases over time
  - 5-year LRR risk (age ≥70 years) **~20%** for low/no adherence



Matar et al. 2022 Ann Surg Oncol

Recent changes in RT

- When most of these trials were set up RT was delivered over 3-5 weeks to the whole breast
- In modern days, good evidence that:
  - **Partial breast RT** is non-inferior in this low-risk group
  - **Ultrahypofractionation** (26 Gy in 5 fractions) is non-inferior to 40 Gy in 15 fractions in terms of efficacy nor side effects (FAST Forward)

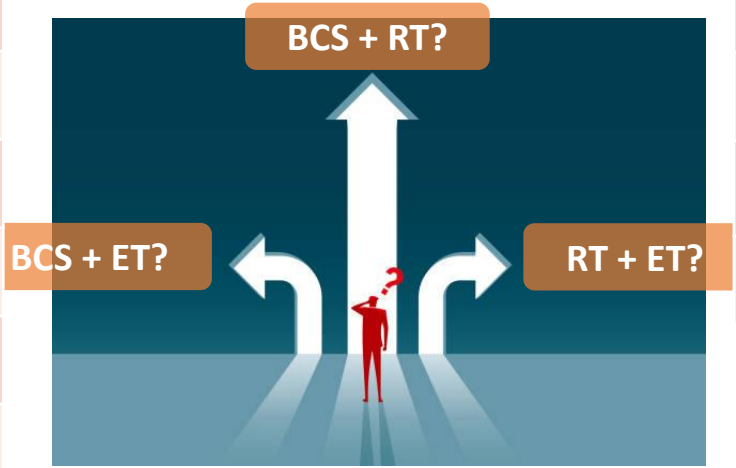
Some patients may prefer 5 fractions instead of taking 5 years of endocrine therapy??

Coles et al. 2017 Lancet

RT or ET Omission in Low-Risk Patients?

EUROPA trial

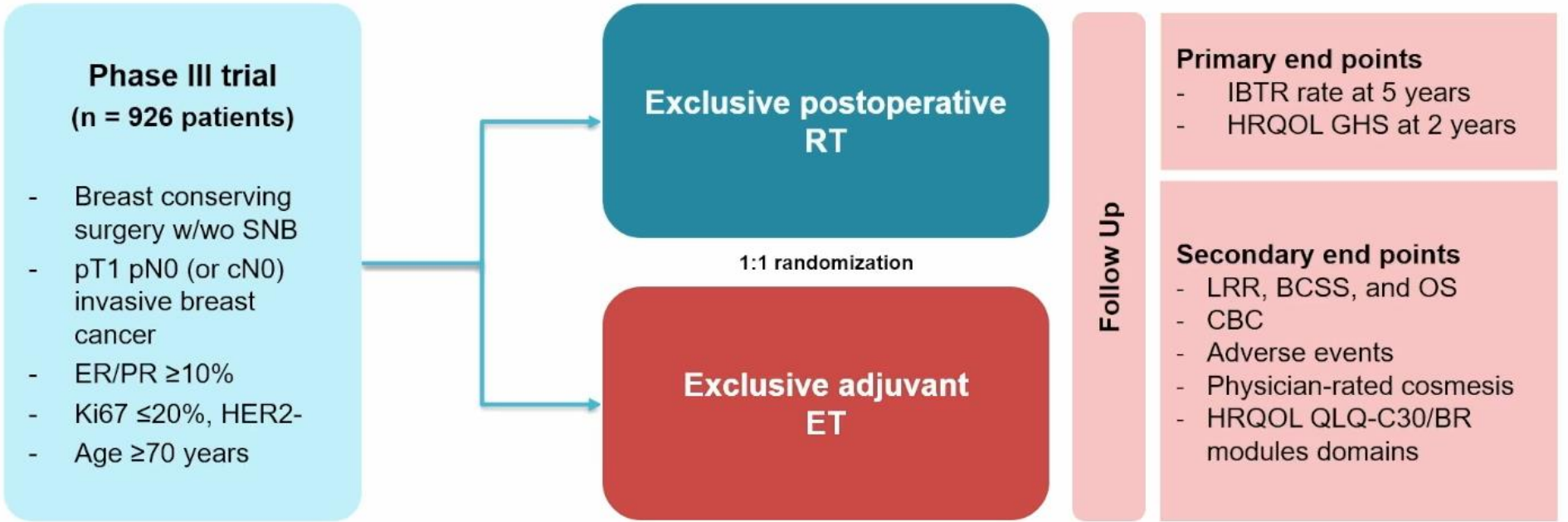
Endocrine therapy
Hot flushes **50 - 67%**
Arthralgia **33 – 38%**
Weight gain **38%**
Mood disturbances **20%**
Nausea **10 - 25%**
Cardiac events **2 – 4%**
Second non breast MA **3 - 14%**
Vascular death (stroke, PE, cardiac) 2-3%



Radiation therapy
Breast shrinkage **7-11%**
Breast induration **5-10%**
Breast oedema **1-4%**
Symptomatic lung fibrosis **0.3-0.9%**
Cardiac events **0.6-0.9%**
Second non breast MA **2-3%**

EUROPA trial

"RT or ET Omission in Low-Risk Patients" ?



EUROPA trial

"RT or ET Omission in Low-Risk Patients" ?

- **Pre-planned interim-analysis at 2 years**
  - RT group: 85% PBI
  - ET group: 89% AI's

RT associated with beter HRQoL compared to HT
Less treatment AE in RT arm
No data on disease controle

EUROPA trial

"RT or ET Omission in Low-Risk Patients" ?

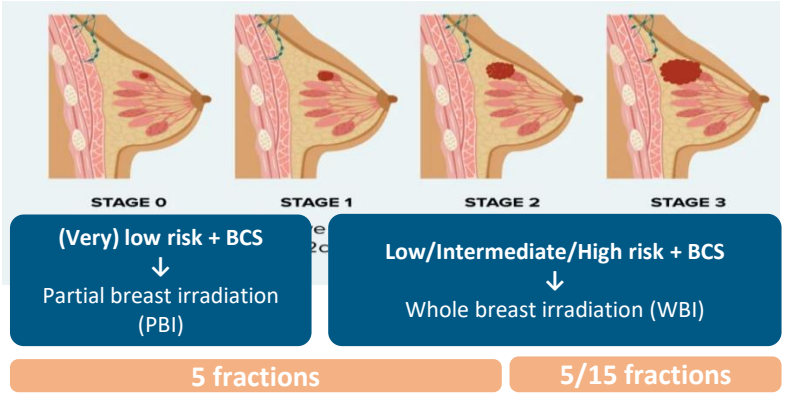
	RT (n = 97)			ET (n = 89)		
Adverse event, n (%)	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4
Arthralgia (Joint pain)	28 (28.9)	0	0	62 (69.7)	5 (5.6)	1 (1.1)
Fatigue	32 (33)	0	0	40 (44.9)	2 (2.2)	0
Breast pain	37 (38.1)	0	0	8 (9)	0	0
Hot flashes	10 (10.3)	0	0	29 (32.6)	2 (2.2)	0
Myalgia (Muscle pain)	13 (13.4)	0	0	28 (31.5)	2 (2.2)	0
Bone pain	23 (23.7)	0	0	25 (28.1)	2 (2.2)	0
Alopecia (Hair loss)	7 (7.2)	0	0	23 (25.8)	0	0
Depression	15 (15.5)	1 (1)	0	21 (23.6)	1 (1.1)	0
Insomnia	15 (15.5)	0	0	21 (23.6)	0	0
Osteoporosis	3 (3.1)	0	0	20 (22.5)	0	0
Hypercholesterolemia	0	0	0	17 (19.1)	0	0
Vaginal dryness	7 (7.2)	0	0	17 (19.1)	0	0
Irritability	15 (15.5)	0	0	12 (13.5)	1 (1.1)	0
Arthritis	15 (15.5)	0	0	14 (15.7)	0	0
Constipation	14 (14.4)	1 (1)	0	12 (13.5)	1 (1.1)	0
Weight gain	12 (12.4)	0	0	12 (13.5)	0	0
Headache	9 (9.3)	0	0	10 (11.2)	0	0
Hypertension	9 (9.3)	0	0	9 (10.1)	0	0

22.5% switched ET
12.4% stopped ET

Lower incidence of treatment-related AEs in the RT arm (67% vs 86%)

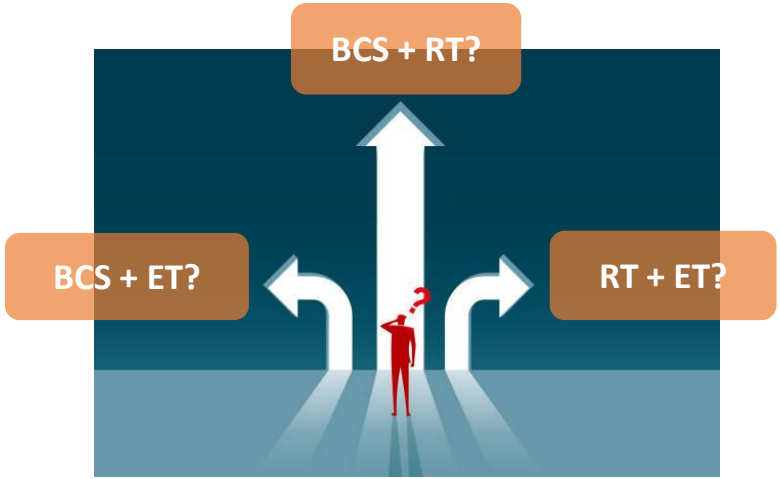
Summary

- Less fractions: **5 x 5,2 Gy standard of care** for breast RT <u>without</u> regional lymph nodes



- Less volume: in well-selected patients **partial breast irradiation** is given

- In well-selected patients: **short course RT may be an alternative to ET**



Thank you!