Development and validation of a nomogram for predicting local relapse in patients undergoing full dose intraoperative radiotherapy with electrons

IEO
Istituto Europeo
di Oncologia

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Arc
Advanced Radiotherapy Center
Il meglio della cura con i raggi intelligenti

IOERT PBI: a tale of

Many benefits

- Therapeutic
- Social
- Economic
- Psycological

Many concerns

- Locoregional control
- Side effects
- Cosmetic outcome

Practical Radiation Oncology® (2024) 14, 112–132

Practice Guideline

Partial Breast Irradiation for Patients With Early-Stage Invasive Breast Cancer or Ductal Carcinoma In Situ: An ASTRO Clinical Practice Guideline

Appropriate PBI techniques with respect to rates of IBR

KQ2 Recommendation	Strength of Recommendation	Quality of Evidence (refs)
5. For patients with early-stage invasive breast cancer receiving PBI, electron IORT is **not** recommended, unless part of a clinical trial or multi-institutional registry.	Strong	Moderate [37]

Given the increased patient convenience of completing RT at the time of surgery…
and the possibility of patient informed preference for IOERT or kV-IORT
even in the setting of a potential for higher risk of IBTR…
investigation into a preferable IORT approach warrants further study

It remains to be defined if more optimized patient selection criteria and treatment techniques will make IORT a recommended option.

The Breast 76 (2024) 103759

Contents lists available at ScienceDirect

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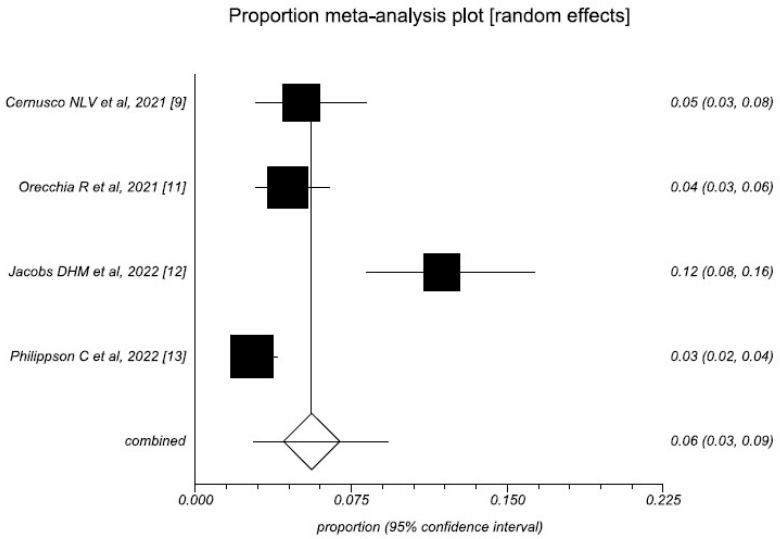
journal homepage: www.journals.elsevier.com/the-breast

A systematic review and meta-analysis of intraoperative electron radiation therapy delivered with a dedicated mobile linac for partial breast irradiation in early breast cancer☆

Cynthia Aristei [a,b,*], Federico Camilli [a,1], Valeria Epifani [a,1], Simona Borghesi [c], Isabella Palumbo [a,b], Vittorio Bini [d], Philip Poortmans [e,f]



Intraoperative radiation therapy alone is associated with a higher IBR rate compared with WBI.

Overall LR rate ranges 0-11.3%

Pooled proportion of 3.8%

5-year probability of 6%

Phase III trials	Cumulative incidence of LR rate	
	5-year	8-10 years
GEC-ESTRO	1.4%	3.5%
IMPORT LOW	0.5%	-
DANISH PBI	1.2%	3.1%
RAPID	-	3%
NSABP B-39	-	4.6%
Florence	1.5%	3.7%

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ELIOT TRIAL

< 1 cm, G1, K-67<14% Luminal A

>2 cm, ≥4 N+, G3, Triple negative

«….IOERT could be discussed on a case-by-case basis and offered to fully informed patients so they can weigh the risks and benefits and participate knowledgeably in shared decision-making…. *«(Orecchia et al 2022)*

	N° studies [REF]	N° lesions	%
T stage **			
pT0	7 [6,7,9,11,20,21,23]	3	0.054
pT1	14 [6–9,11-14,20,21,23,25–27]	4514	82.32
pT2 - pT3	14 [6–9,11-14,20,21,23,25–27]	494	9.00
pT3	10 [6–9,13,20,23,25–27]	3	0.054
Not Reported		390	7.11
N stage**			
pN0	14 [6–9,11-14,20,21,23,25–27]	4309	78.58
pN1 – pN2	14 [6–9,11-14,20,21,23,25–27]	790	14.40
pN2	11 [6,8,9,11,13,14,20,23,25–27]	175	3.19
Not Reported		384	7.00
Tumour Biopathological Characteristics			
ER +	12 [6,7,8,9,10,11,12,13,14,22,23,25]	4512	–
ER	9 [6,7,9–11,13,14,22,25]	423	–
PgR +	9 [6–9,11,13,14,22,25]	3363	–
PgR	9 [6,7,9,11,13,14,22,23,25]	970	–
ER and/or PgR +	3 [20,21,27]	164	–
ER and/or PgR	3 [20,21,27]	11	–
Not Described	2 [26,28]	–	–
Ki67 < 14 %	2 [6,25]	758	–
Ki67 ≥ 14 %	2 [6,25]	1198	–
Ki67 </≤ 20 %	4 [7,11,13,23]	1259	–
Ki67 >/≥ 20 %	4 [7,11,13,23]	606	–
Ki67 ≤ 30 %	1 [10]	176	–
Ki67 > 30 %	1 [10]	101	–
Not Described	10 [8,9,12,14,16,20,12,22,26,27]	–	–
HER2 +	12 [6–11,13,14,20,22,24,25,27]	426	–
HER2	14 [6–14,20,22,23[a],25,27]	4516	–
Not Described	3 [21,26,28]	–	–

Practical Radiation Oncology (2017)

Accelerated Partial Breast Irradiation: Update of an ASTRO Evidence-Based Consensus Statement

Candace Correa, MD,[1] Eleanor E. Harris, MD, [2] Maria Cristina Leonardi, MD,[3] Benjamin D. Smith, MD,[4] Alphonse G. Taghian, MD, PhD,[5] Alastair M. Thompson, MD,[6] Julia White, MD,[7] Jay R. Harris, MD[8]*

Factors associated with LR among 585 patients who received ELIOT (per protocol)

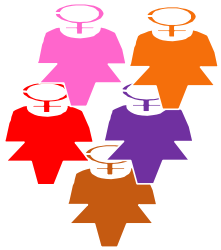
	Patients	IBTR	Cumulative incidence			Univariate analysis	
Characteristics	n	n	5-year	10-year	15-year	HR (95% CI)	p value
ASTRO criteria [12]							
Suitable	211	25	2.1 (0.8- 4.6)	6.4 (3.7-10.0)	14.1 (8.8-20.6)	1.00	
Cautionary	166	19	6.0 (3.1-10.0)	10.4 (6.5-15.3)	10.4 (6.5-15.3)	1.05 (0.58-1.91)	0.87
Unsuitable	140	22	6.2 (3.2-10.7)	10.0 (6.0-15.3)	16.3 (10.3-23.5)	1.35 (0.76-2.40)	0.30

to obtain an individualized risk estimate of LR that can assist ROs and patients in choosing electron IORT PBI

The primary endpoint of the nomogram was the prediction of the in-breast tumor recurrence (IBTR) rate

Nomogram Construction and validation

The Training set



3,397 subjects treated with IOERT PBI between January 2000 and December 2016, outside ELIOT trial

Eligibility: female gender, first diagnosis of breast cancer, breast-conserving surgery, and 21 Gy full-dose IOERT

Follow-up updated until December 2021

The Validation set

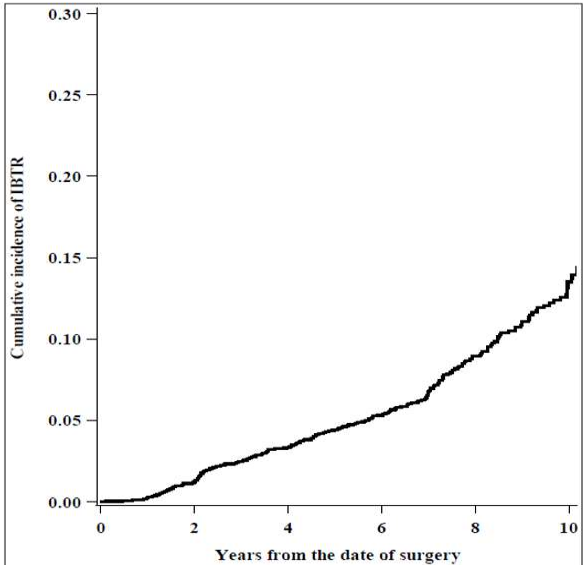
586 subjects included in the ELIOT study
Per protocol analysis
Between Nov 20, 2000, and Dec 27, 2007

Follow-up updated until March 2019

Cumulative incidence of IBTR (N=3397) -Median FU (Q1-Q3) in years: 6.1 (4.3-8.0)

The training set

222 isolated IBTR,
43 IBTR + synchronous event (33 N+, 6 DM, 4 contralateral BC)

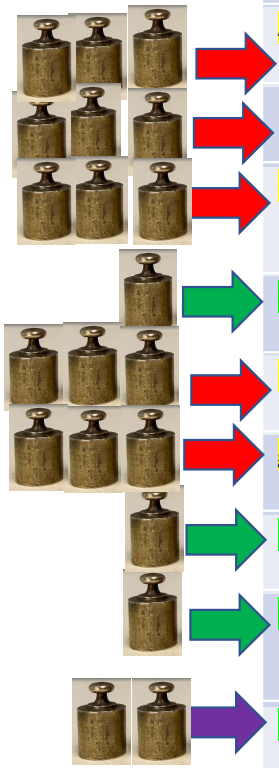


Events	Competing events	Censored	1-y CIF (95% CI)	3-y CIF (95% CI)	5-y CIF (95% CI)	10-y CIF (95% CI)
265 (7.8%)	388 (11.4%)	2744 (80.8%)	0.3 (0.1-0.5)	2.5 (2.0-3.1)	4.4 (3.7-5.2)	13.5 (11.7-15.5)

Competing events: Regional node *Mets (N=37), contralat BC (N=58), bone Mets (N=26),visceral merts (20), brain mets (N=2), other (N=1), multiple mets (N=36), primary non breast tumor (N=141), death as first event (N=67),*

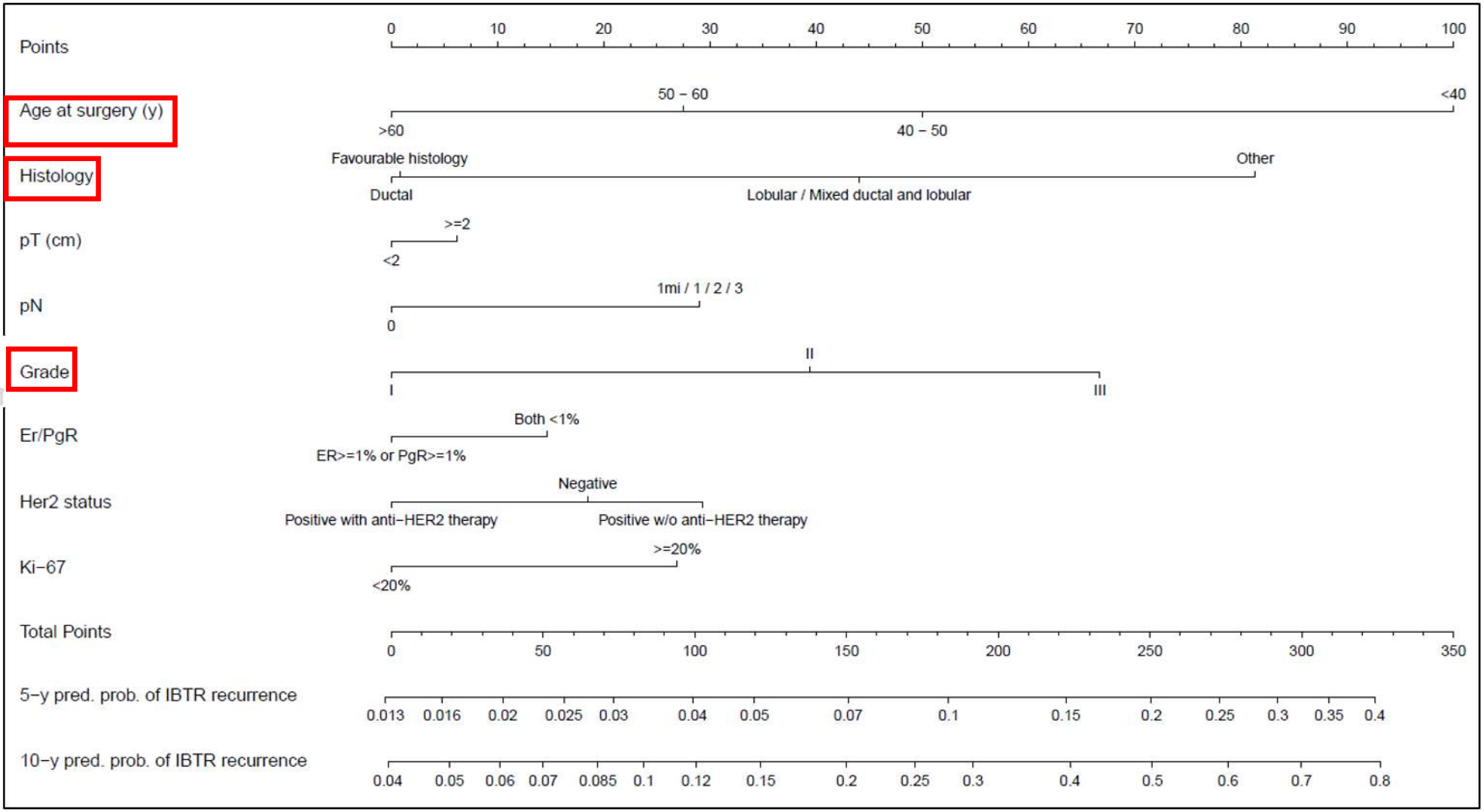
Competing events: 5-y CIF (95% CI): *7.8 (6.8-8.7) ;* ***10-y CIF (95% CI):*** *17.4 (15.4-19.4)*

Association patient/tumor characteristics and risk of IBTR, according to the Fine and Gray regression model



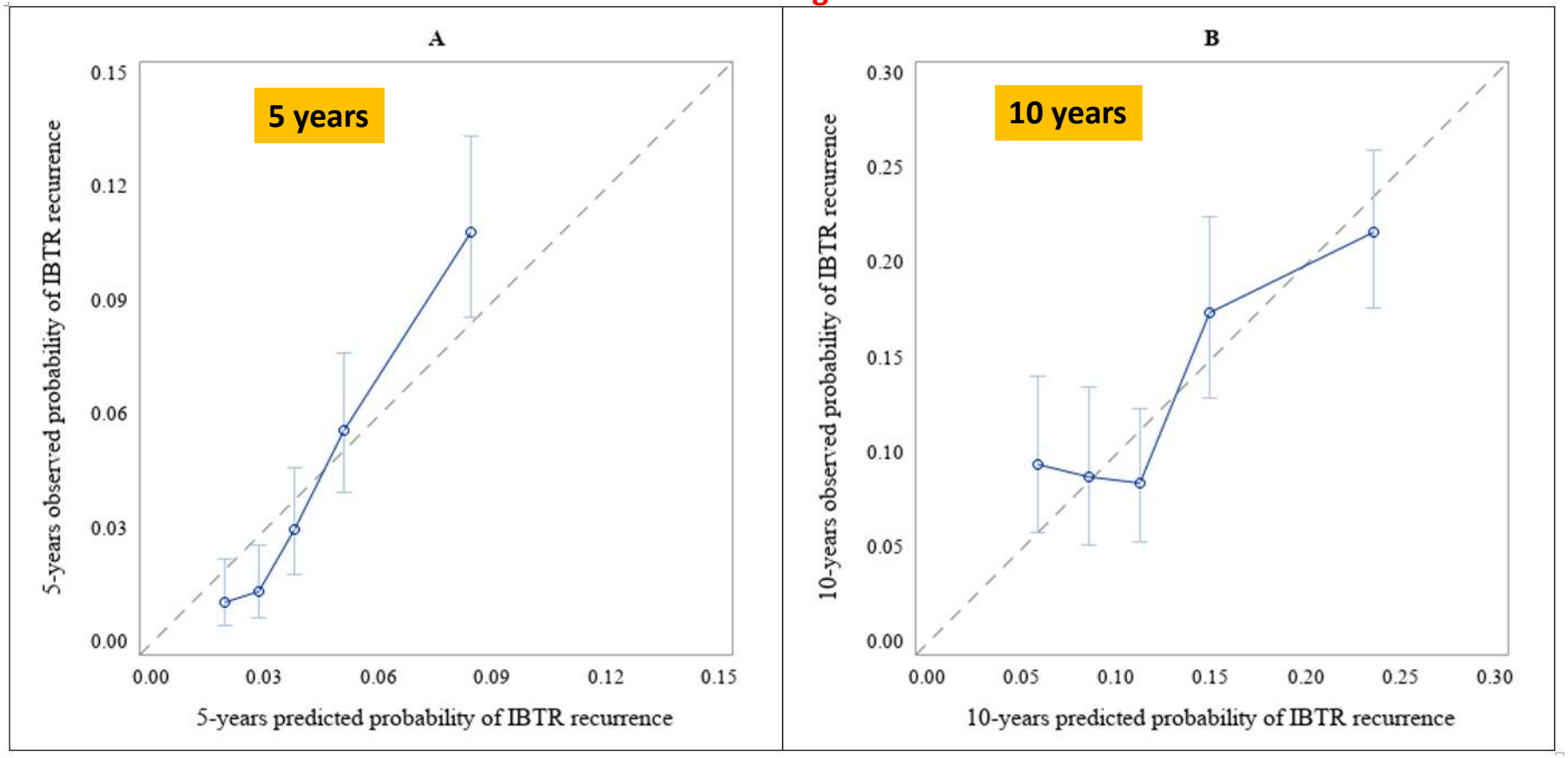
	level	UNIVARIATE		MULTIVARIATE	
variables	Level	HR	p	HR	p
Age at surgery	>60 <60	Ref 1.36	<0.029	Ref 1.36	<0.031
Menopausal status	Pre post	Ref 0.68	0.004		
Histology	Ductal Lobular/mixed Favorable histologies	Ref 1.36 0.62	0.058 0.18	Ref 1.64 1-01	0.004 0.98
pT	<2 ≥2	Ref 1.52	0.012	Ref 1.07	0.71
pN	Negative positive	Ref 1.63	<0.001	Ref 1.39	0.019
grade	1 3	Ref 3.13	<0.001	Ref 2.12	0.005
ER/PgR	Both <1% positive	Ref 0.53	<0.001	Ref 0.85	0.45
HER2	Negative Positive no anti HER2 Positive + anti HER2	Ref 2.19 1.09	0.002 0.74	Ref 1.13 0.81	0.68 0.43
Ki67	<20% ≥20%	Ref 1.98	<0.001	Ref 1.35	0.087
Subtype	Luminal A Luminal B HER2 no anti HER2 HER2 + antiHER2 Triple neg	Ref 1.95 2.97 1.60 2.65	<0.001 0.017 0.36 <0.001		

Nomogram for predicting 5-year and 10-year probability of IBTR, according to MV Fine and Gray regression model



Calibration plots: predicted vs. observed 5-years (Panel A) and 10-years (Panel B) probability of IBTR

The Training set



Harrell's c-index: 0.69 (95% CI: 0.66 - 0.73)

The predictive performance of the nomogram was internally validated.

The validation set

585 subjects randomized to receive IOERT within the phase III randomized ELIOT trial (per-protocol analysis)

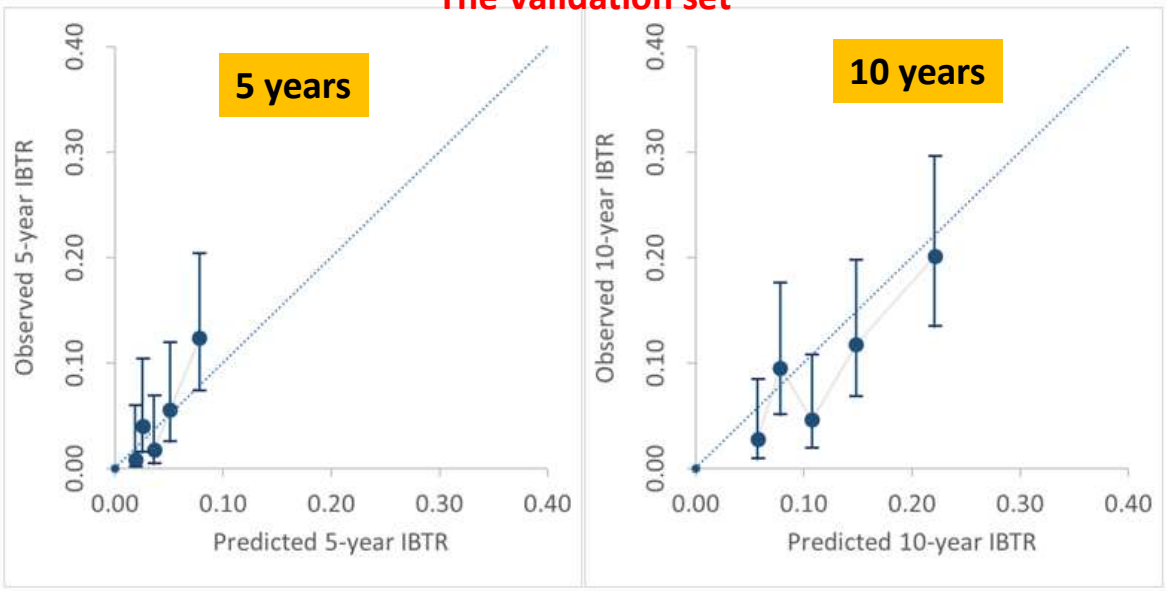
follow-up updated to March 2019 (median follow-up time of 12.4 years)

	5-year event rate (95%CI)	10-year event rate (95%CI)
Ipsilateral breast tumor recurrence	**ELIOT group (per protocol analysis)**	
	4.5% (3.0%-6.3%)	**8.6% (6.5%-11.1%)**
	TRAINING SET	
	4.4% (3.7%-5.2%)	**13.5% (11.7%-15.5%)**

Characteristics		Training N (%)	Validation N (%)	P-value
		3397 (100.0)	585 (100.0)	
Age				
	<60	1606 (47.3)	293 (50.1)	
	>60	1791 (52.7)	292 (49.9)	0.21
Histology				
	Ductal	2715 (79.9)	480 (82.1)	
	Lobular	380 (11.2)	50 (8.5)	
	Ductal and lobular	75 (2.2)	15 (2.6)	
	Other	227 (6.7)	40 (6.8)	0.28
Pathological size				
	≤2 cm	3019 (88.9)	516 (88.2)	
	>2 cm	371 (10.9)	69 (11.8)	0.54
	Missing	7	-	
Positive nodes				
	pN0	2590 (76.2)	438 (74.9)	
	pN+	716 (21.1)	147 (25.1)	0.06
	Missing	91	-	
Tumour grade*				
	G1	948 (27.9)	181 (30.9)	
	G2	1645 (48.4)	274 (46.8)	
	G3	733 (21.6)	118 (20.2)	0.31
	Missing	71	12	
Oestrogen Receptor (ER)				
	Absent	311 (9.2)	55 (9.4)	
	Present	3085 (90.8)	530 (90.6)	0.85
	Missing	1	-	
Progesterone receptor (PgR)				
	Absent	682 (20.1)	142 (24.3)	
	Present	2713 (79.9)	442 (75.6)	0.02
	Missing	2	1	
Proliferative index (Ki-67)				
	≤20%	2145 (63.1)	363 (62.1)	
	>20%	1244 (36.6)	221 (37.8)	0.60
	Missing	8	1	
Her2				
	0/+/++	3000 (88.3)	533 (91.1)	
	Over-expressed	310 (9.1)	51 (8.7)	0.63
	Missing	87	1	
Molecular Subtype				
	Luminal A	2018 (59.4)	226 (38.6)	
	Luminal B	983 (28.9)	304 (52.0)	
	HER2 positive (non-luminal)	88 (2.6)	16 (2.7)	
	Triple negative	216 (6.4)	39 (6.7)	<0.001
	Missing	92	-	
Adjuvant treatment				
	Control	58 (1.7)	16 (2.7)	
	Endocrine therapy alone	2762 (81.3)	449 (76.8)	
	Chemotherapy alone	277 (8.2)	47 (8.0)	
	Endocrine and chemotherapy	300 (8.8)	73 (12.5)	0.01

Calibration curves of the nomograms predicting the 5-year and 10-year cumulative incidence of IBTR in 585 patients who received intraoperative radiotherapy in the ELIOT trial (per protocol analysis)

The Validation set



Quintile of risk	Observed 5-year IBTR	Predicted 5-year IBTR	Observed 10-year IBTR	Predicted 10-year IBTR
Q1 (n=117)	1	2.2	3	6.7
Q2 (n=105)	4	2.7	9	8.2
Q3 (n=119)	2	4.3	5	12.8
Q4 (n=114)	6	5.8	12	16.9
Q5 (n=114)	13	8.9	20	25.2
Total (n=569*)	26	23.9	49	69.8
Hosmer & Lemeshow Goodness of fit	Chi square = 4.59 with 4 DF (P=0.47)		Chi square = 9.37 with 4 DF (P=0.052)	

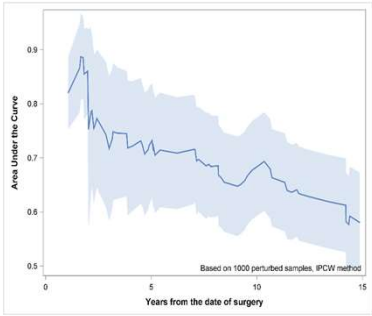
Harrell's Concordance Statistic =0.638

Conclusions

- **Included variables that can be available at the time of IOERT delivery to provide individualized risk estimates allowing for assisting the decision-making**

- **The C-index of 0.638 is concordant with multiple other nomograms used in BC management**

Figure 2. Time dependent AUC



Harrell's Concordance Statistic =0.638

- **Monoinstitutional setting→bias by the single-centre practice clinical patterns**

- **External validation is needed**

We are all apprentices in a craft where no one ever becomes a master

Ernest Hemingway