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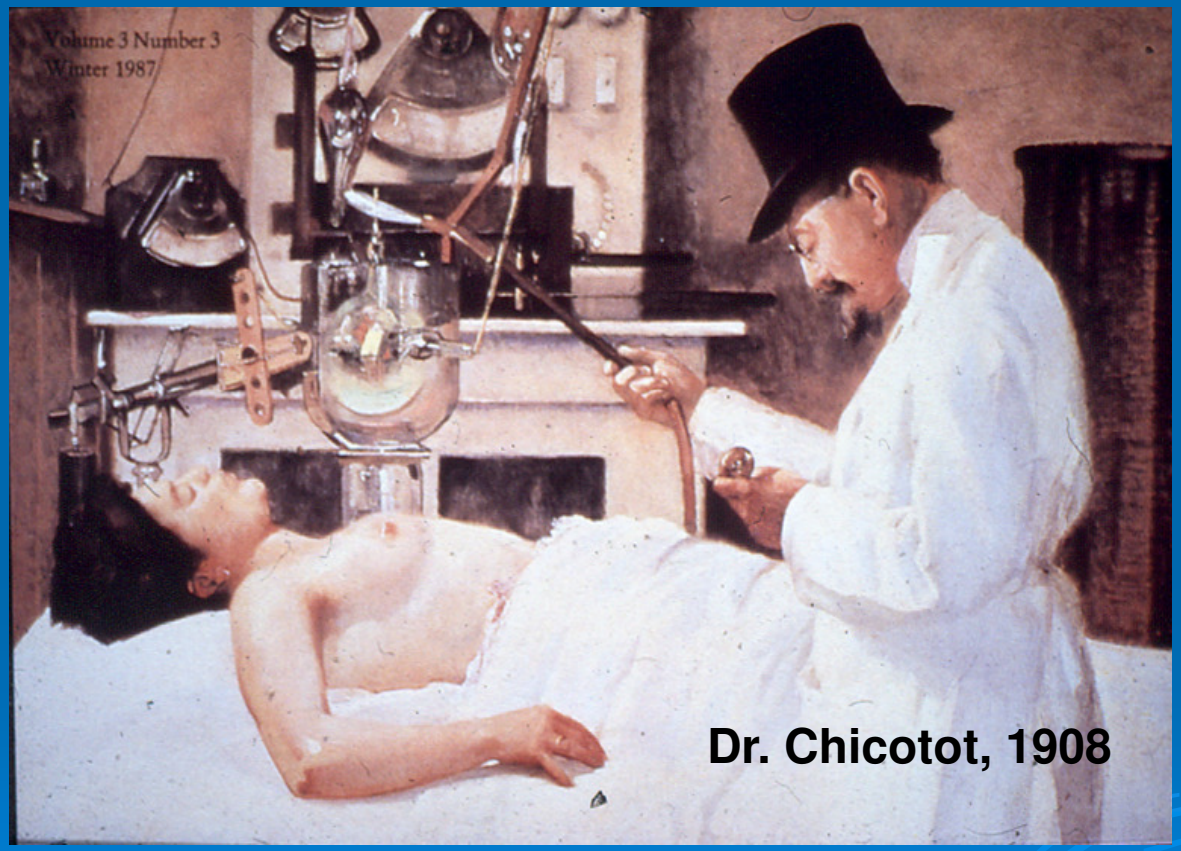
Radiotherapy of early breast cancer, status on Danish trials



Dr. Chicotot, 1908

Birgitte Vrou Offersen
Overlæge, lektor, ph.d.
Aarhus University Hospital

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Moderately hypofractionated adjuvant radiotherapy of early breast carcinoma

CIRRO protocol IP030209
Hypofractionated *versus* standard fractionated whole breast irradiation to lymph-node negative breast cancer patients: a randomized phase II study (DBCG HYPO)

CIRRO protocol IP030109
Partial *versus* whole breast irradiation to women ≥ 60 years operated with breast conservation for low risk breast cancer: a randomized phase II study (DBCG PBI)

CIRRO protocol IP030315
Hypofractionated *versus* standard fractionated loco-regional radiotherapy of early node-positive breast cancer: a randomized phase II study (DBCG HYPO II, Skagen Trial 1)

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Randomization

stratification: institution, breast size 600 ml, systemic therapy and boost

Woman >40 years
c. mammae
pT1-2, pN0(mi+),
ER/PgR +/-,
Grade I, II, III,
HER2 +/-,
Carc. in situ

50 Gy / 25 fractions

40 Gy / 15 fractions

Start May 2009

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Endpoints / Follow up

Primary endpoint:
≥ grade 2 breast induration after 3 years

Secondary endpoints:
Specialist and patient evaluated cosmesis.
Genetic risk profile for late morbidity.
Recurrence and localisation of recurrence, death and cause of death

Follow up:
•Cosmesis and photos
•Translational protocol ⟶ 1 skin biopsy at inclusion and blood samples at every morbidity evaluation

Frequency: Morbidity evaluation + blood sample at baseline and year 1-5 and 10 after RT, thus 7 times per patient

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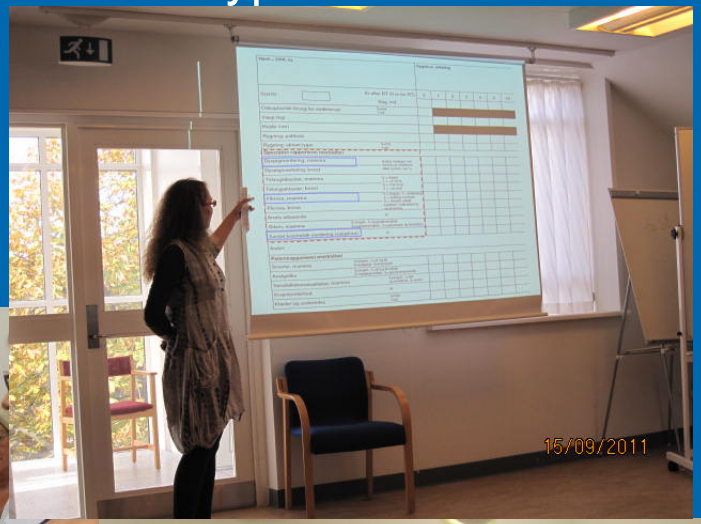
Workshop every year

- All recruiting centres participate, reproducibility is tested in selected patients with different types of late morbidity.



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Protocol assumptions

- 3 years after RT, grade 2-3 breast induration is expected in the following 3 subgroups as
  - 8% for ”RT only” patients
  - 10% for ”RT + Endocrine” patients
  - 15% for ”RT + Chemotherapy”

  - 10% for all patients on trial

Danish Breast Cancer Cooperative Group, DBCG

Statistics

Basis:

80% power, 5% level of significans, onesided test, accept up to 10% difference

DBCG PBI

Expected frequency of ≥ grade 2 fibrosis after 3 years is 8% in the whole cohort

Thus calculated need of 314 patients or 33 events

If constant inclusion is assumed there will be around 1000 patients included in the study when 314 patients have been followed 3 years

DBCG HYPO

Expected frequency of ≥ grade 2 fibrosis after 3 years is 10% in the whole cohort

Thus calculated need of 338 patients or 44 events

If constant inclusion is assumed there will be around 1000 patients included in the study when 338 patients have been followed 3 years, thus the effect of systemic therapy on morbidity may be evaluated

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Characteristics of 316 pts with 3 yr follow up

-online meeting DBCG RT committee Mar 26th, 2014

- N=316 patients with full status 3 yr post RT

	Aarhus	Aalborg	Vejle	Odense
N	200	36	18	62

Number of patients followed for 3 yr on Mar 26th, 2014: 336

Number of pts needed with 3 yr data before closure: 338

Thus, accrual stopped Mar 26th, 2014

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Characteristics on 316 pts with 3 yr follow up

	40 Gy / 15 fractions	50 Gy / 25 fractions
Frequence	160 (50.6%)	156 (49.4%)
Boost	26 (16.3%)	25 (16.0%)
RT only (122 pts)	58	64
RT + ET (70 pts)	39	31
RT + CT (124 pts)	63	61
Oncoplastic surgery	15 (9%)	10 (6%)
Current smoker at 3 yr	23 (14%)	35 (22%)

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Breast induration

	Grade					
	0	1	2	3	9	Total
Year 3	150	134	28	3	1	316
	47%	42%	9%	1%		

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Breast induration by RT regimen

Year 3	Grade					
	0	1	2	3	9	Total
40 Gy	78	65	15	1	1	160
	49%	41%	9%	0.5%	0.5%	
50 Gy	72	69	13	2	0	156
	46%	44%	8%	1%		

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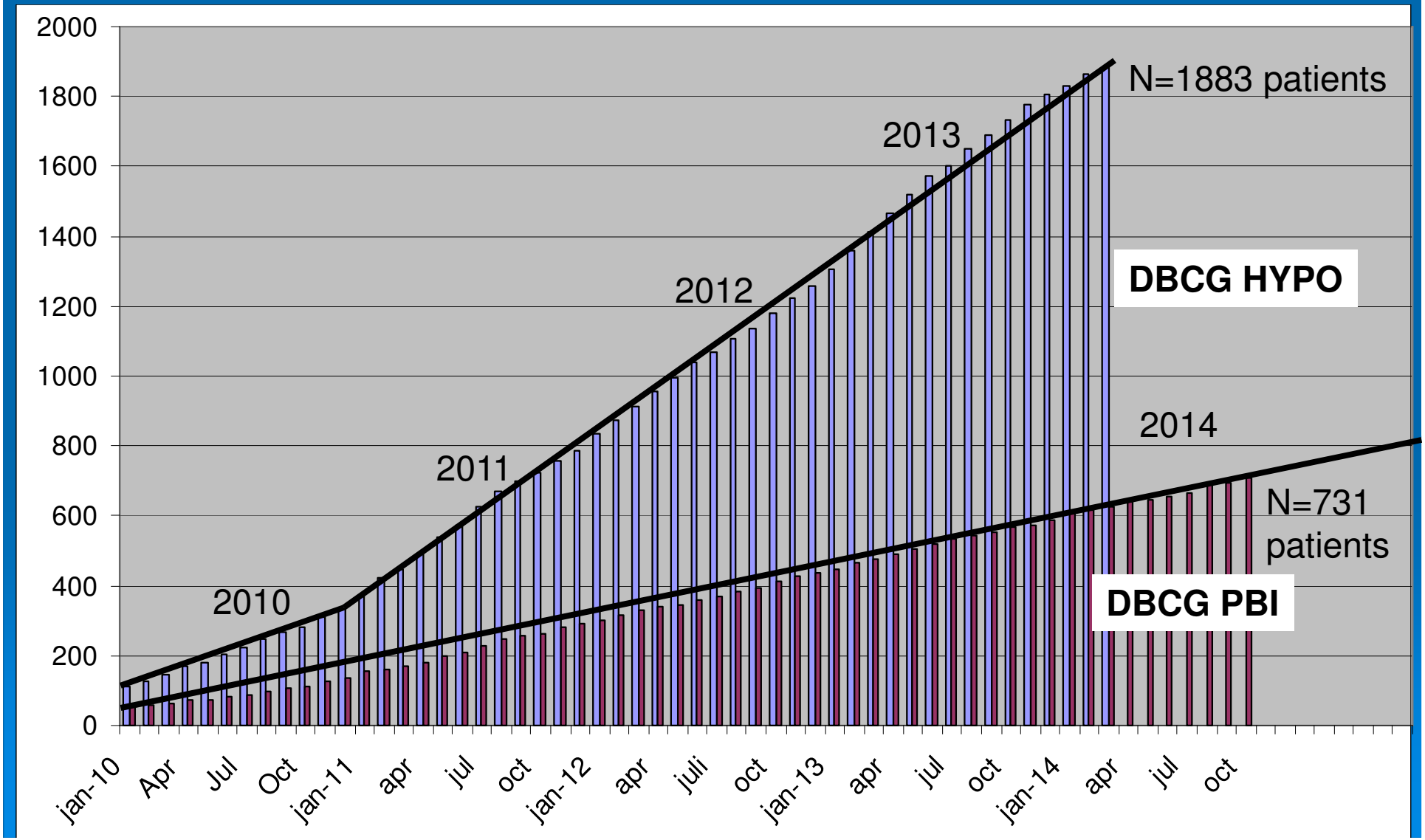
Status of the DBCG RT protocols by Jan 1th 2015



Status DBCG HYPO

- Closed Mar 27th, 2014 with 1883 patients
- Data on morbidity, QA of RT, nationwide dose plan bank, effect of respiratory gating
- Substudies are planned
- Ph.d.project on genetic risk profile for late RT related morbidity (1000 skin biopsies and sequential yearly blood samples)
- Change of DBCG guideline as of Mar 27

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Rationale for Partial Breast Irradiation PBI

- Natural history for breast cancer indicates most local recurrences close to or in the tumor bed
- We are able to select patients with very low risk of local recurrence
- Short treatment time / waiting lists
- Preference of the breast cancer patients

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Randomized phase III studies*

Study	N	Experimental RT	Start
NSABP B-39 / RTOG 0413	4300 T≤3 cm, pN1, All ages	34 Gy / 10 fr with interst. Brachy, MammoSite, 3D-CRT	March 2005
RAPID / OCOG	2128, ≥40 years, T<3 cm, pN0, non-lob.	38.5 Gy / 10 fr with 3D-CRT	January 2006
GEC-ESTRO	1170 ≥40 years, T≤3 cm, ≤1 micromet in axilla	32 Gy / 8 fr or 30.3 Gy / 7 fr with Interst. Brachy or 50 Gy PDR	May 2004
IMPORT-LOW	1935, ≥50 years, T≤2 cm, pN0 (single cell-pN1), grade I/II, non-lob.	40 Gy / 15 fr with 3D-CRT or 40 Gy / 15 fr to tumor bed + 36 Gy / 15 fr to the surrounding breast	Sept. 2006
ELIOT	824, Quadr.ectomy, >48 years, ≤2.5 cm, pN0	Intraop 21 Gy electrons	December 2000
TARGIT	1600 Pragmatic, non-lob.	Intraop 20 Gy, 50 kV	March 2000

*at start 2009

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Inclusion criteria DBCG PBI

- Radical lumpectomy
- Unifocal, unilateral non-lobular c.mammae
- ≥60 years
- pT1 and pN0
- Grade I and II
- ER +
- HER2 -

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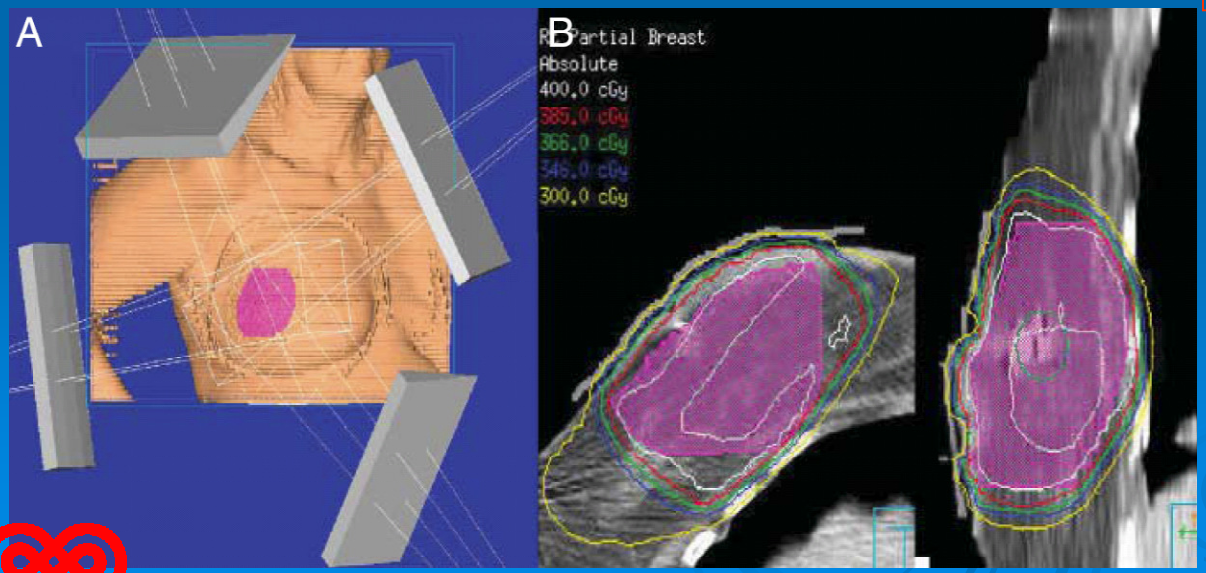
Randomization

stratified for endocrine therapy and institution

40 Gy / 15 frac.
3 weeks

→ **Partial breast**

→ **Whole breast**



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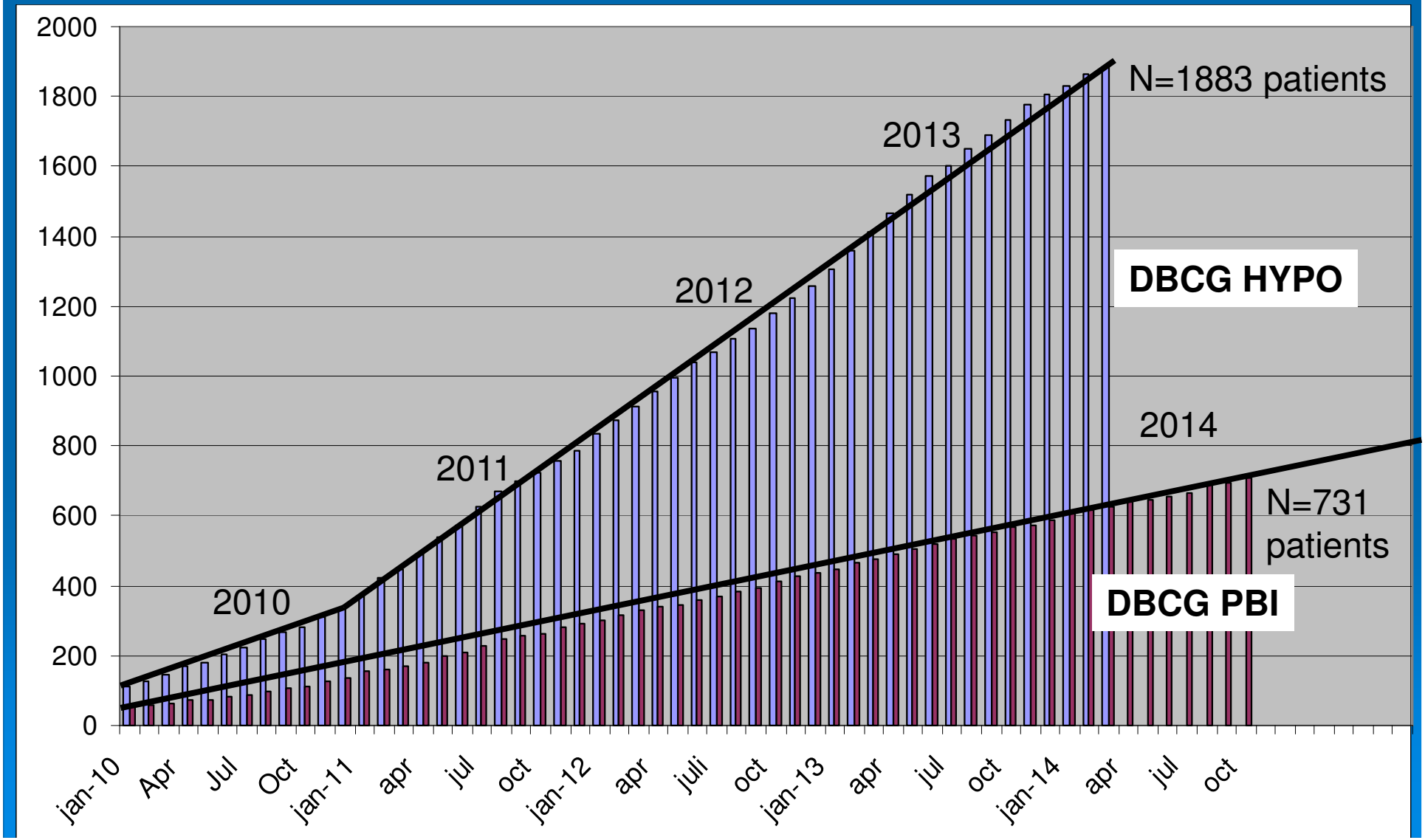

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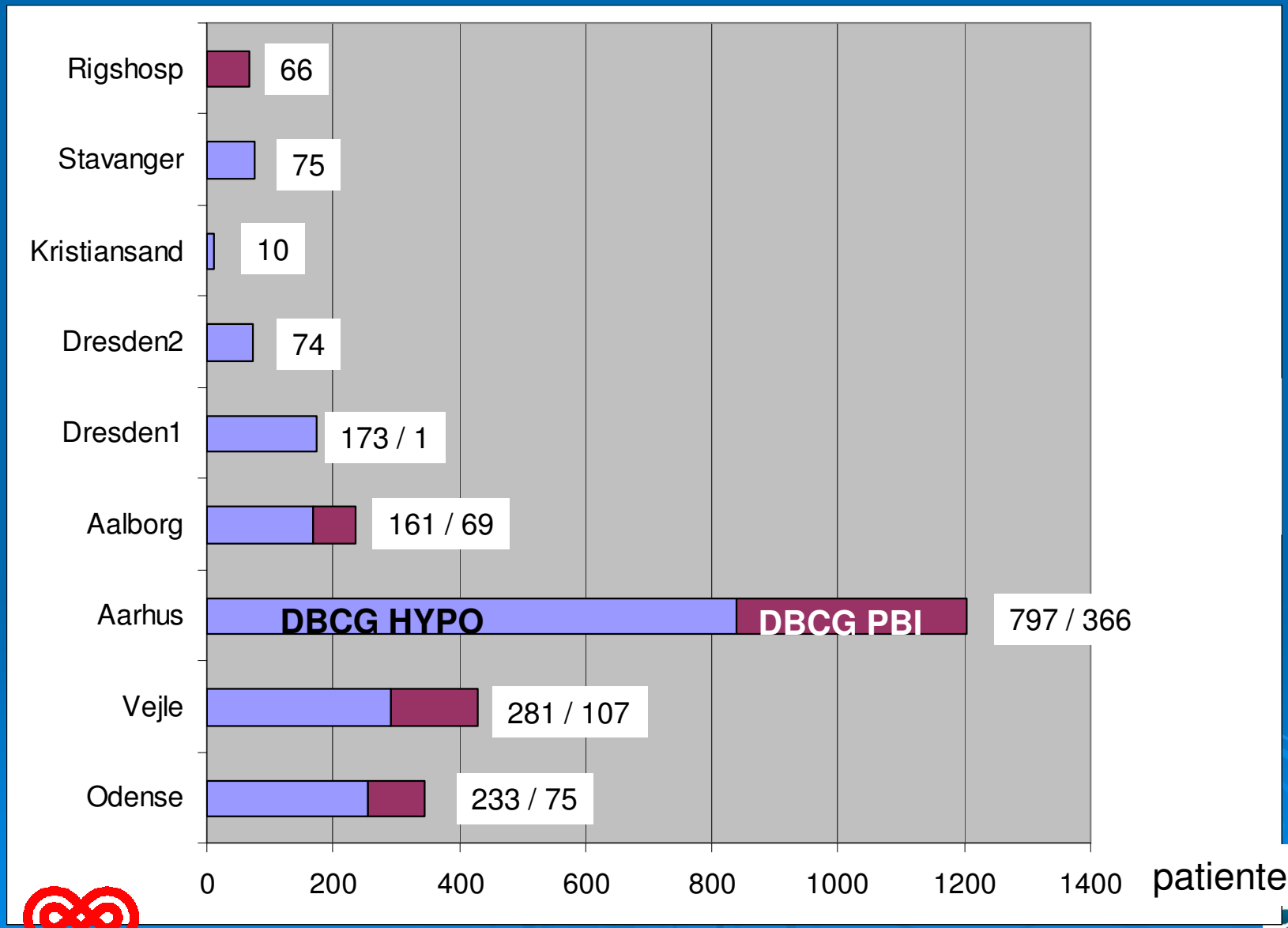

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Status DBCG PBI

- Expected accrual reached Spring 2015
- First reporting will take place at EBCC 2016 together with the IMPORT LOW and the GEC-ESTRO Trial

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DBCG HYPO II, The Skagen Trial 1

- 75% of all Danish adjuvant RT treatments are residual breast RT only. The majority of these are now based on 40 Gy/15 fr
- 25% of our pts are candidates for loco-regional RT, which in most countries are provided as 50 Gy / 25 fr
- The UK and Holland have started loco-reg RT based on 40 Gy / 15 fr
- In Holland they provide boost as SIB (simultaneous integrated boost) as standard

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AIM

- Assure a systematic and quality-controlled introduction of moderately hypofractionated loco-regional breast RT based on 40 Gy/15 fr in Denmark
- Introduce simultaneous integrated boost

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Randomization

stratification: institution, surgical type, systemic therapy

Woman ≥18 years
c. mammae
pT1-3, pN1-3,
ER/PgR +/-,
Grade I, II, III,
HER2 +/-,
Primary syst therapy,
breast implant, connective tissue disease accepted

50 Gy / 25 fractions

40 Gy / 15 fractions

If she is a boost candidate, the boost will be provided as a SIB shortening the overall treatment time with 5 days

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Endpoints

- Primary: arm lymphedema
- Secondary: DBCG morbididy as previously used incl photos, PROM a.m. Gärtner, ROM, use of sleeve, recurrence (where and when)

This will take place before RT, then yearly 1-5 and 10

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Statistics

- Null hypothesis: hypofractionated RT does not increase the risk of lympedema 3 yr after RT compared to normofractionated RT
- Lymphedema is ≥10% increased arm circumference 15 cm above / 10 cm below olecranon
- Cross-sectional study in Aarhus, 2007-12, 277 pts (ALND, taxane, reg RT 50 Gy) showed 10% with lymphedema median 3 yr FU
- We expect 10% risk of lymphedema, accept a 5% increase, 80% power, 1-sided test, 5% sign level, 5% yearly drop out rate, 3 yr accrual and 3 yr follow up
- Thus we need 131 events or 1012 patients with 3 yr follow up
- Accrual continues until 131 events/1012 pts are followed for 3 yr
- Thus potential for >2000 pts included

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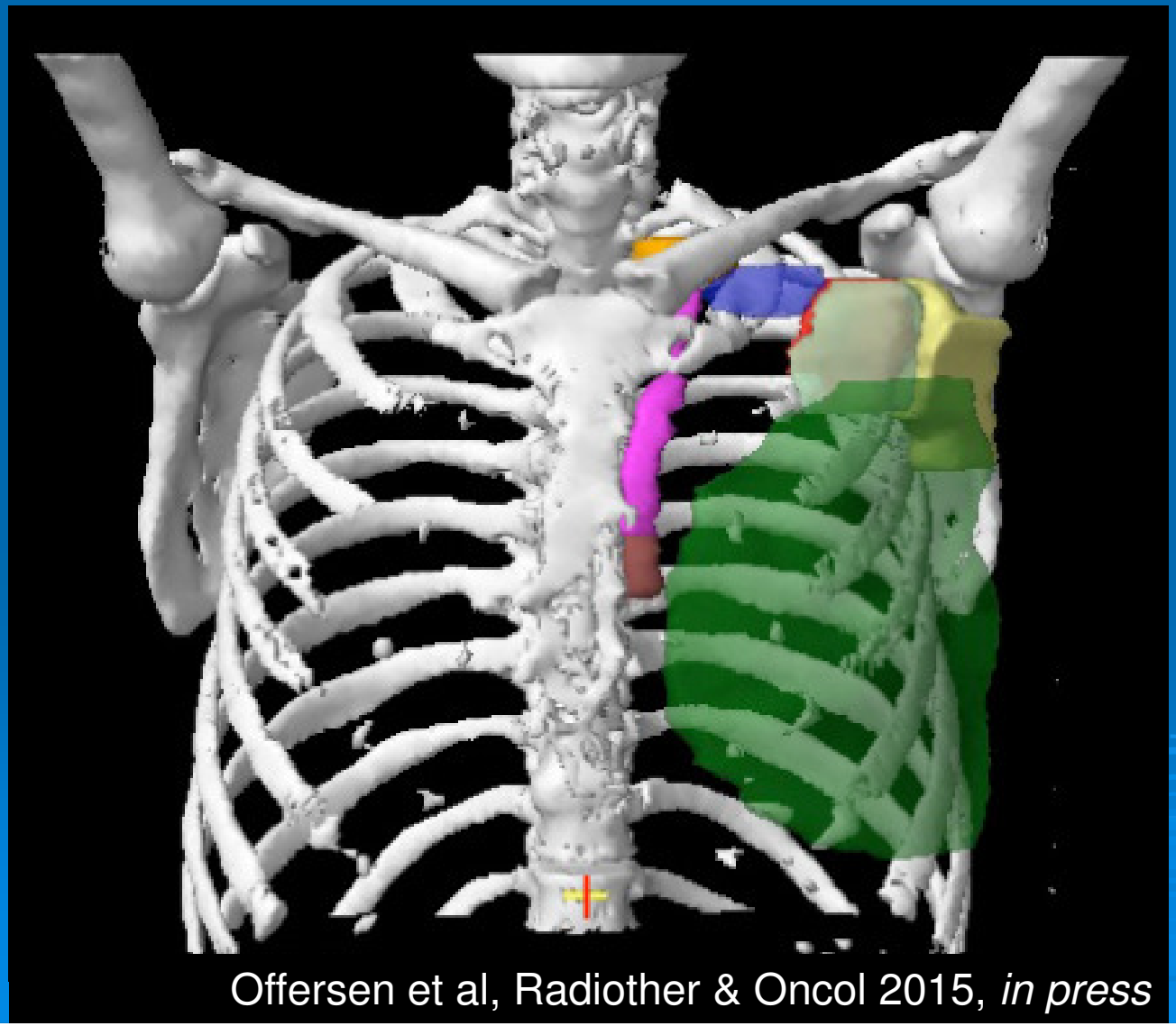
DBCG HYPO II
The Skagen Trial 1



Offersen et al, Radiother & Oncol 2015, *in press*

Localisation of reg recurrences

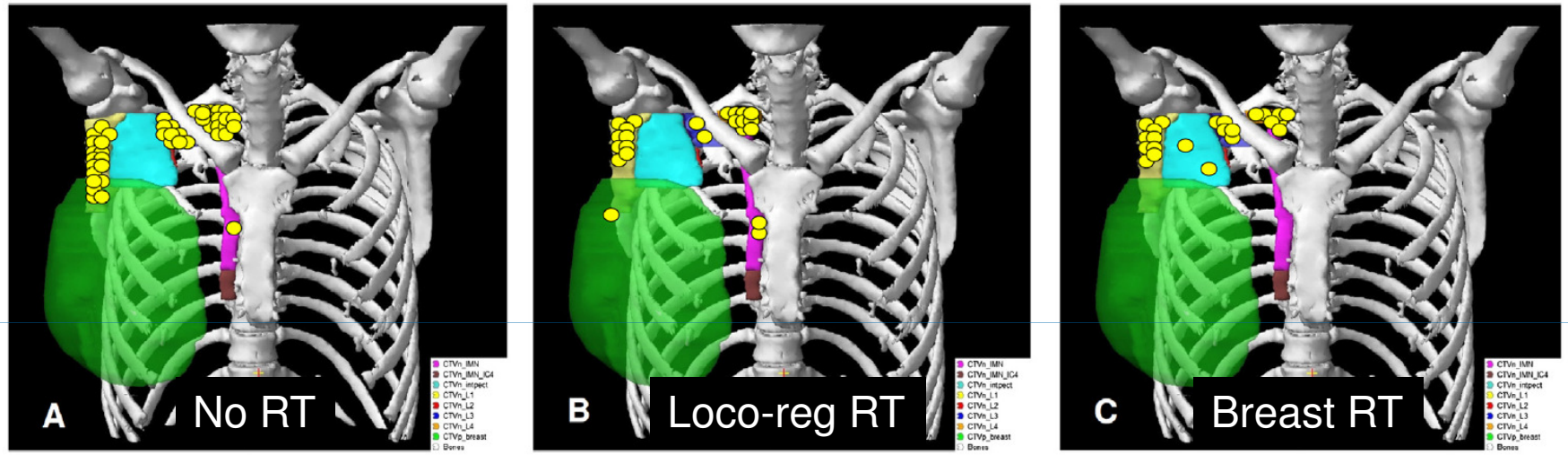


Fig. 1. 73 patients were diagnosed with a total of 101 regional recurrences (RR). The primary breast cancer diagnosis and adjuvant treatment took place from 1991 to 2013. The median time from diagnosis to RR was 3.7 years. At the time of RR, some patients had a diagnostic CT and/or MR scan performed and in these patients the localisation of their RR was delineated in the dose planning system if the former RT plan was 3D based. In case of former 2D planning, the RT documentation photos were reviewed. The rest of the RR was diagnosed after clinical evaluation and ultrasound, and those descriptions were used. (A) RR after no adjuvant RT (38 patients with 53 RR). Half of these patients had node positive disease at diagnosis and thus an indication for loco-regional RT, which was not given due to patient preference or co-morbidity. The most common localisation of RR was multiple lesions in axilla levels I, III, and/or in the lymph node level IV (ESTRO nomenclature (10)). (B) RR after adjuvant loco-regional RT based on 48–50 Gy/24–25 fractions (21 patients with 25 RR). The RT field edges used respected the humeral head, and included the medial 2/3 of the clavicular bone. Cranially the field edges corresponded to the lower edge of the cricoid cartilage and medially it respected a radio-opaque wire positioned alongside the anterior edge of the sternocleidomastoid muscle. In CT-based dose plans, the nodal areas were dosed to ⩾90% dose, whilst in the 2D era the dose was 95–96.5% in 4 cm depth depending on energy. For patients with >6 positive nodes, the dose in the mid-axillary level was ⩾90%. Most patients failed in axilla level I and in lymph node level IV. Regarding the radiation coverage of the RR areas, only one of the 21 patients failed outside the field, namely very caudal in the axillary level I, and she had 17 positive nodes. In general the area of RR was covered by at least 95% of the prescribed dose. None of the lymph node level IV recurrences were located medial to the jugular vein, and recurrences in axilla level I were located ventrally. (C) RR after adjuvant whole breast RT (14 patients with 23 regional recurrences). The RR were most often seen in axilla level I.

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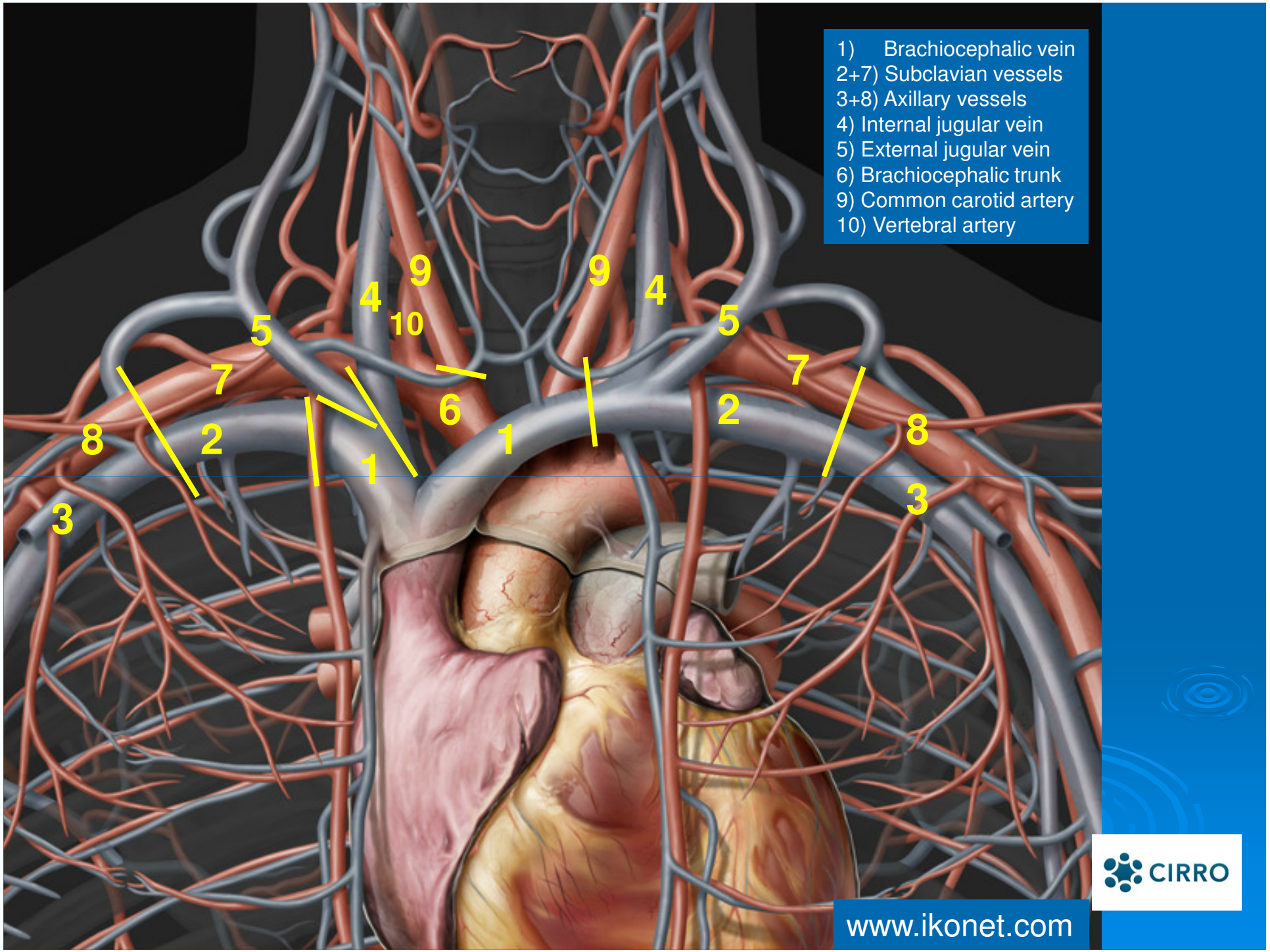
Melgaard & Offersen, Radiother & Oncol 2015, *in press*


1) Brachiocephalic vein
2+7) Subclavian vessels
3+8) Axillary vessels
4) Internal jugular vein
5) External jugular vein
6) Brachiocephalic trunk
9) Common carotid artery
10) Vertebral artery
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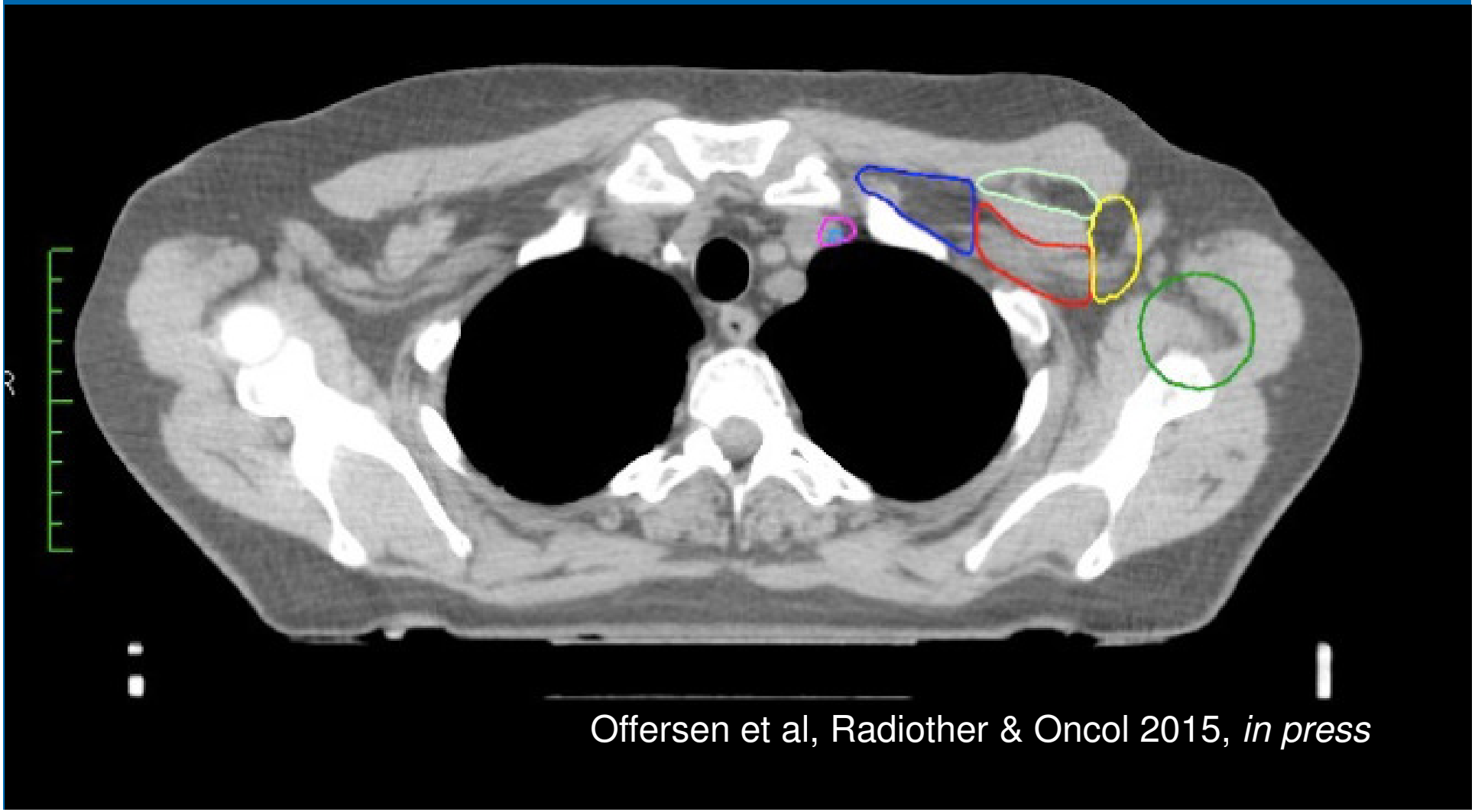
ESTRO delineation consensus



Offersen et al, Radiother & Oncol 2015, *in press*

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SIB

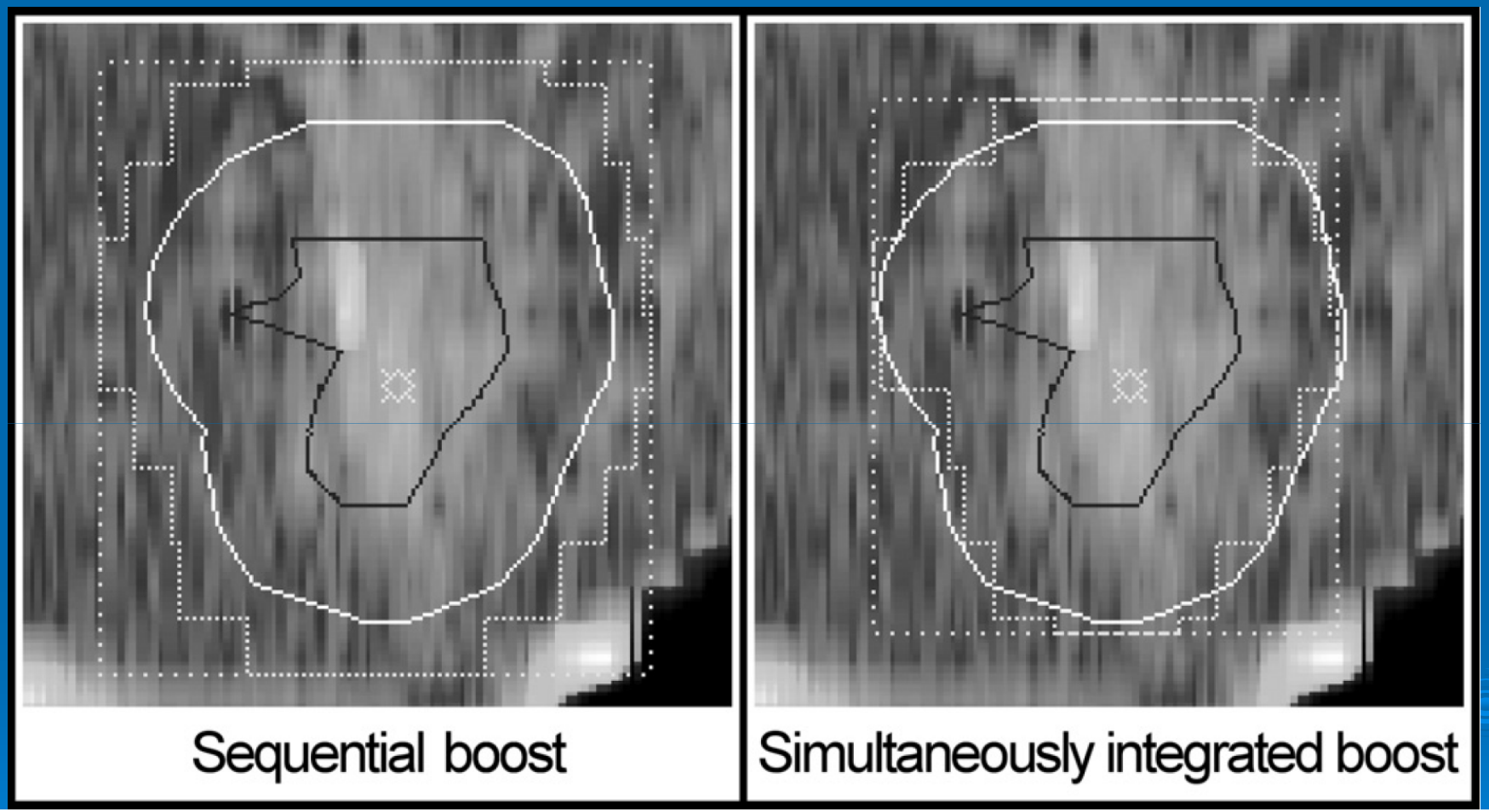

Fig. 1. Reconstructed radiograph from boost beam's-eye-view with sequentially planned and simultaneously integrated boost. With simultaneously integrated boost technique, multileaf collimator shielding (short dotted lines) can be applied without use of margins around boost planning target volume (white solid line), resulting in substantial reduction of excess volumes irradiated.

van der Laan et al, IJROBP 68: 1018-1023, 2007

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BED(2 Gy)-based doses for SIB

Randomisation arm	Standard boost	SIB / non-SIB breast / fr
50 Gy / 25 fr	16 Gy / 8 fr	63 Gy / 51.52 Gy / 28 fr
50 Gy / 25 fr	10 Gy / 5 fr	57 Gy / 50 Gy / 25 fr
40 Gy / 15 fr	16 Gy / 8 fr	52.2 Gy / 42.3 Gy / 18 fr
40 Gy / 15 fr	10 Gy / 5 fr	45.75 Gy / 40 Gy / 15 fr

Participating centres

- All 8 Danish RT departments
- Germany: Dresden x2, Tübingen, (Flensburg)
- Poland: Gliwice
- France: Inst Curie
- Belgium: Namur, Brussels
- Norway: Stavanger, Tromsø
- Italy: Firenze
- Slovenia: Ljubljana
- Australia: Sydney
- More depts consider to participate….

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Current status

- Ethical committee
- Datatilsynet
- DBCG

- Hope to start Febr 2015

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Thanks

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