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Hypofractionated Versus Standard Fractionated Radiotherapy in Patients With Early Breast Cancer or Ductal Carcinoma In Situ in a Randomized Phase III Trial: The DBCG HYPO Trial

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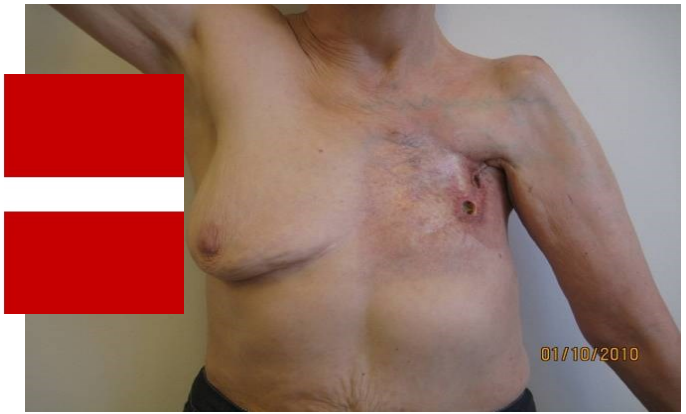
Journal of Clinical Oncology 2020

Ingen interessekonflikter

Baggrund DBCG HYPO

Moderat hypofraktionering 36-42 Gy / 12 fr DBCG standard indtil 1982



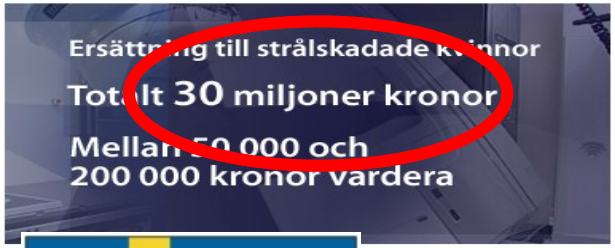
Strålebehandling 1980
Foto 2010,
30 år senere

Besvär efter åtta år

En av de drabbade, Marianne Mosserud, berättade för Aktuellt om hur besvären i armen som började åtta år efter bröstoperationen nu gör henne allt mer handikappad.

Marianne Mosserud

-Jag kan ju inte lyfta ett papper ens. Jag kan inte knipa ihop med fingrarna. Jag kan inte.
Är det nånting som jag ska bära, så får jag ta det i munnen.
Och det är ju svårt med tunga saker...
Ett papper kan man ju ta, nån filt eller så, berättade Marianne.



Komiteens tilråding

Komiteen viser for øvrig til proposisjonen og det som står foran, og rår Stortinget til å gjøre følgende

vedtak:

I statsbudsjettet for 1998 gjøres følgende endring:

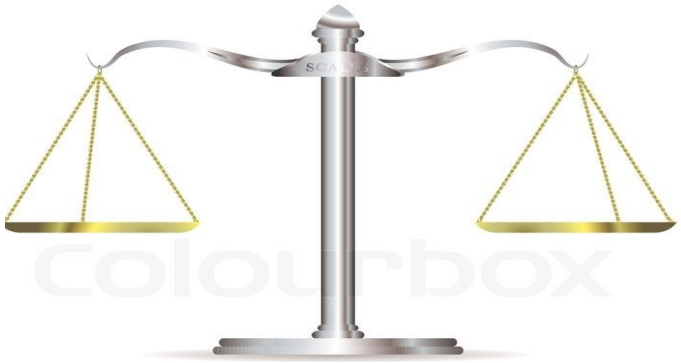
Kap. 739	Andre utgifter			
	73 (ny)	Erstatning for stråleskader, *kan overføres,*		
		bevilges med	kr	85000000

#DKD2021

Baggrund DBCG HYPO

Positive resultater fra

- **Canada (2002)**
- **UK START Trials A & B (2008)**
- **Moderne RT teknikker**
- **Ventelister lange**



Dårlige DBCG erfaringer før 1982

Begrænsede data fra patienter med

- **boost**
- **stor bryststørrelse**
- **moderne systemisk behandling**

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Formål DBCG HYPO

Formål

- Reintroducere moderat hypofraktioneret adjuverende bryst strålebehandling (RT) til lymfeknude-negative brystkræftpatienter på en kontrolleret og systematisk måde i Danmark

Hypotese

- Brug af 40 Gy / 15 fr (2.67 Gy / fr) ved brystbestråling resulterer ikke i mere grad 2-3 fasthed i brystet efter 3 år sammenlignet med 50 Gy / 25 fr

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Randomisering

Invasiv tidlig brystkræft / DCIS, ≥41 år

Brystbevarende operation

pTis-pT2, pN0-pN1(mic)

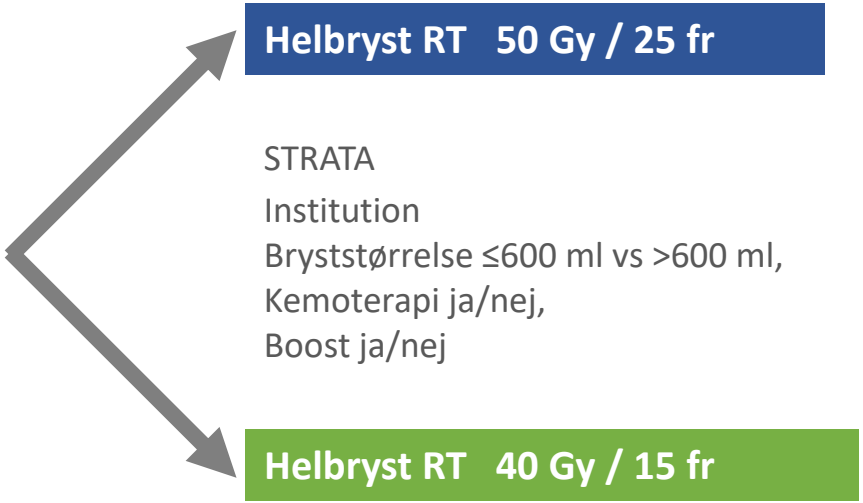
Enhver histologi / ER / HER2 / grad

Boost tilladt

Alle bryststørrelser

Enhver systemisk behandling

Brystimplantater ikke tilladt



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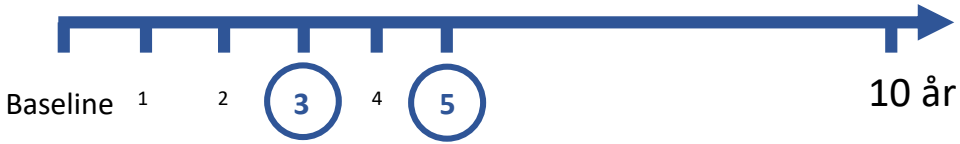
Endepunkter

Primære

- **Grad ≥2 brystfasthed efter RT (ved 2 eller flere opfølgninger)**

Sekundære

- Andre RT-relaterede bivirkninger
- Body image scale og fotos af bryster (ikke rapporteret)
- Patienttilfredshed
- Tilbagefald, incl type, hvor, hvornår



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Status for inklusion af patienter

	50Gy/25fr	40Gy/15fr
All	949	933
Aarhus	420	418
Vejle	149	142
Odense	132	121
Aalborg	82	85
Dresden, Gustav Carus	84	89
Dresden-Friedrichstadt	36	38
Stavanger	39	37
Kristiansand	7	3

Inklusion Maj 2009 - Mar 2014

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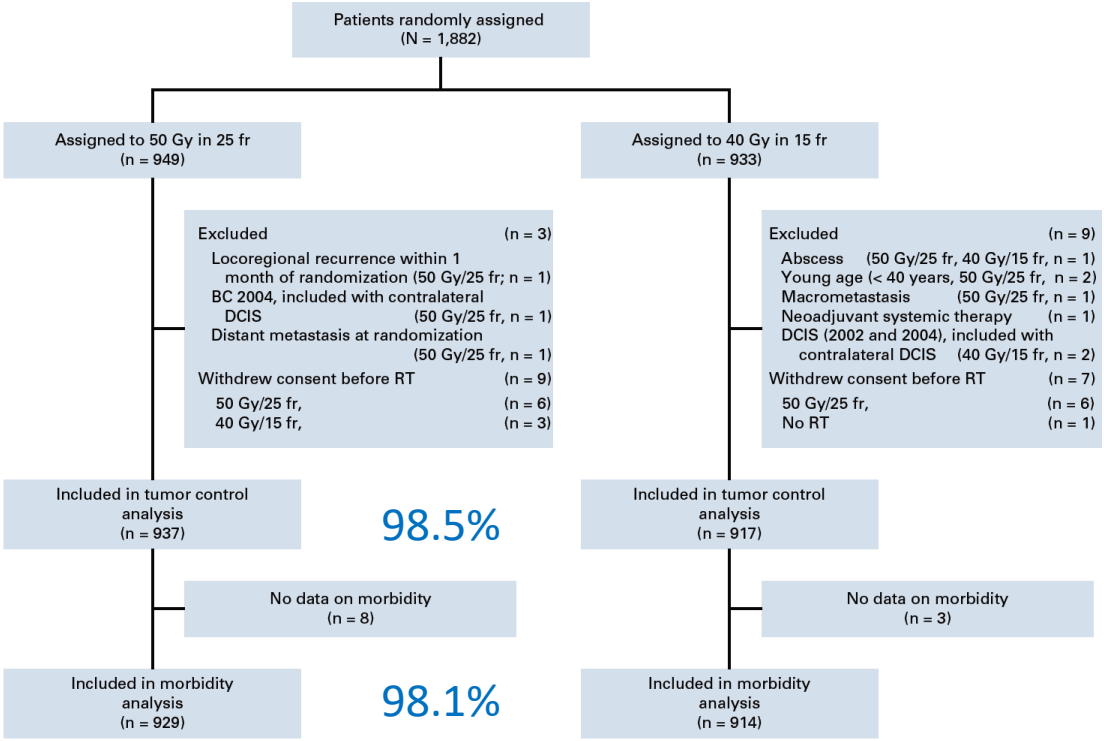
Consort diagram



5-års bivirkninger indberettet for 1452 patienter (77%) *Offersen BV et al, J Clin Oncol 2020*

Baseline karakteristika

Characteristic	50 Gy in 25 Fractions (n = 937)	40 Gy in 15 Fractions (n = 917)
Age, years		
Median (range)	59 (42-83)	59 (41-82)
41-49	101 (11)	98 (11)
50-59	389 (42)	383 (42)
60-69	349 (37)	351 (38)
70-83	98 (10)	85 (9)
Breast size, mL (CTVp_breast)		
≤ 600	420 (45)	425 (46)
> 600	512 (55)	491 (54)
Laterality		
Right	455 (49)	445 (49)
Left	482 (51)	472 (51)
Histology		
DCIS	123 (13)	123 (13)
Ductal	620 (66)	615 (67)
Lobular	97 (10)	104 (11)
Other invasive	97 (10)	75 (8)
Tumor size[a]		
T1a	48 (6)	64 (8)
T1b	196 (24)	191 (24)
T1c	414 (51)	403 (51)
T2	156 (19)	136 (17)
Grade[b]		
1	216 (35)	196 (32)
2	260 (42)	249 (40)
3	139 (22)	164 (7)
Unknown[c]	5 (1)	6 (1)
Lymph nodes[a]		
Negative	661 (81)	683 (86)
Isolated tumor cells	46 (6)	35 (4)
Micrometastasis ≤ 2 mm	107 (13)	76 (8)
ER status[a]		
Negative	114 (14)	123 (15)
Positive	699 (86)	667 (84)
Unknown[c]	1 (0)	4 (1)
HER2 status[a]		
Negative	746 (92)	685 (86)
Positive	63 (8)	92 (12)
Unknown[a]	5 (1)	17 (2)
ER/HER2 status[a]		
ER+/HER2−	647 (79)	592 (75)
ER+/HER2+	48 (6)	60 (8)

Characteristic	50 Gy in 25 Fractions (n = 937)	40 Gy in 15 Fractions (n = 917)
ER−/HER2+	15 (2)	32 (4)
ER−/HER2−	98 (12)	90 (11)
Unknown	6 (1)	20 (3)
Radiotherapy boost, Denmark		
No	659 (85)	645 (86)
Yes	116 (15)	108 (14)
Radiotherapy boost, Germany		
No	18 (15)	20 (16)
Yes	100 (85)	105 (84)
Radiotherapy boost, Norway		
No	44 (100)	38 (97)
Yes	0 (0)	1 (3)
Chemotherapy[a]		
No	465 (57)	461 (58)
Yes	349 (43)	333 (42)
Systemic therapy[d]		
No	198 (26)	192 (25)
Tamoxifen	39 (5)	45 (6)
Letrozole	241 (31)	235 (31)
Chemotherapy	243 (31)	213 (31)
Chemotherapy + trastuzumab	54 (7)	68 (9)
Smoking status		
Never/prior	739 (79)	745 (81)
Current	185 (20)	160 (17)
Unknown	13 (1)	12 (1)

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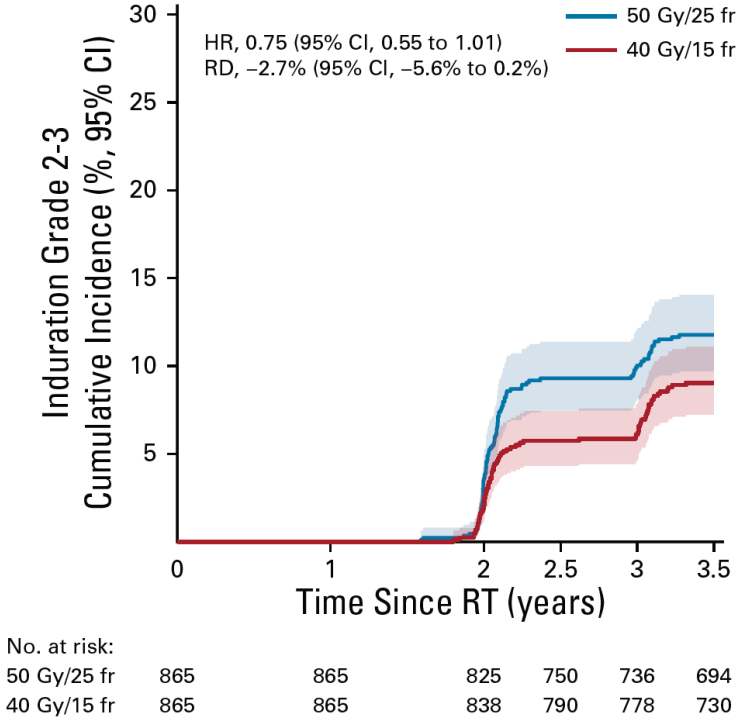
Fasthed i brystet (N=1830)



- Median opfølgning 7.26 år
- I univariat analyse er 40 Gy / 15 fr ikke associeret med øget risiko for fasthed i brystet

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RT relaterede bivirkninger

TABLE 2. Primary and Secondary Morbidity End Points, Odds Ratio for 40 Gy/15Fractions Versus 50 Gy/25 Fractions at Years 3 and 5 and At All Follow-Up Assessments

	Year 3				Year 5				All Follow-Up Assessments			
	No. of Patients With Event/All Patients (%)				No. of Patients With Event/All Patients (%)				No. of Events/Total No. of Assessments (%)			
Event	50 Gy/25 Fractions	40 Gy/15 Fractions	OR (95% CI)	*P*	50 Gy/25 Fractions	40 Gy/15 Fractions	OR (95% CI)	*P*	50 Gy/25 Fractions	40 Gy/15 Fractions	OR (95% CI)	*P*
Induration	105/812 (13)	84/825 (10)	0.76 (0.56 to 1.04)	.082	85/718 (12)	67/734 (9)	0.75 (0.53 to 1.05)	.092	538/4,049 (13)	442/4,091 (11)	0.80 (0.65 to 0.98)	.029
Favorable overall cosmetic outcome	619/812 (76)	672/825 (81)	1.37 (1.08 to 1.74)	.0098	540/718 (75)	590/734 (80)	1.35 (1.05 to 1.73)	.018	3122/4,049 (77)	3317/4,091 (81)	1.22 (1.02 to 1.47)	.032
Telangiectasia	47/812 (6)	53/825 (6)	1.12 (0.75 to 1.68)	.59	67/718 (9)	75/734 (10)	1.11 (0.78 to 1.56)	.57	230/4,049 (6)	276/4,091 (7)	1.14 (0.86 to 1.52)	.35
Dyspigmentation	113/812 (14)	85/825 (10)	0.71 (0.53 to 0.96)	.025	69/718 (10)	51/734 (7)	0.70 (0.48 to 1.02)	.067	669/4,049 (17)	512/4,091 (13)	0.74 (0.62 to 0.88)	< .001
Scar appearance	182/794 (23)	178/821 (22)	0.93 (0.74 to 1.18)	.55	155/692 (22)	143/716 (20)	0.86 (0.67 to 1.12)	.27	872/3,977 (22)	860/4,054 (21)	0.99 (0.83 to 1.19)	.93
Edema	13/812 (2)	9/825 (1)	NA	NA	7/718 (1)	7/734 (1)	NA	NA	90/40,49 (2)	61/4091 (1)	0.62 (0.39 to 0.99)	.044
Pain	46/812 (6)	30/825 (4)	0.63 (0.39 to 1.01)	.053	42/718 (6)	27/734 (4)	0.61 (0.37 to 1.01)	.054	238/4,049 (6)	177/4,092 (4)	0.76 (0.57 to 1.01)	.063
Use of analgesics	8/812 (1)	3/825 (0)	NA	NA	4/718 (1)	4/734 (1)	NA	NA	37/4,049 (1)	39/4,092 (1)	1.12 (0.57 to 2.23)	.74
Sensibility change	67/812 (8)	32/825 (4)	0.45 (0.29 to 0.69)	< .001	47/718 (7)	44/734 (6)	0.91 (0.60 to 1.39)	.66	277/4,049 (7)	206/4,092 (5)	0.73 (0.56 to 0.97)	.028
Patient satisfaction, treated breast	734/804 (91)	748/819 (91)	1.00 (0.71 to 1.42)	.98	645/714 (90)	665/728 (91)	1.13 (0.79 to 1.62)	.51	3531/3,905 (90)	3601/3,947 (91)	1.09 (0.86 to 1.38)	.48
Patient satisfaction, compared with contralateral breast	665/802 (83)	693/819 (85)	1.13 (0.87 to 1.48)	.35	586/713 (82)	613/722 (85)	1.22 (0.92 to 1.61)	.17	3211/3898 (82)	3,325/3,933 (85)	1.15 (0.95 to 1.39)	.14

Ingen forskel eller bedre resultater med 40Gy afhængigt af endepunkt og tid

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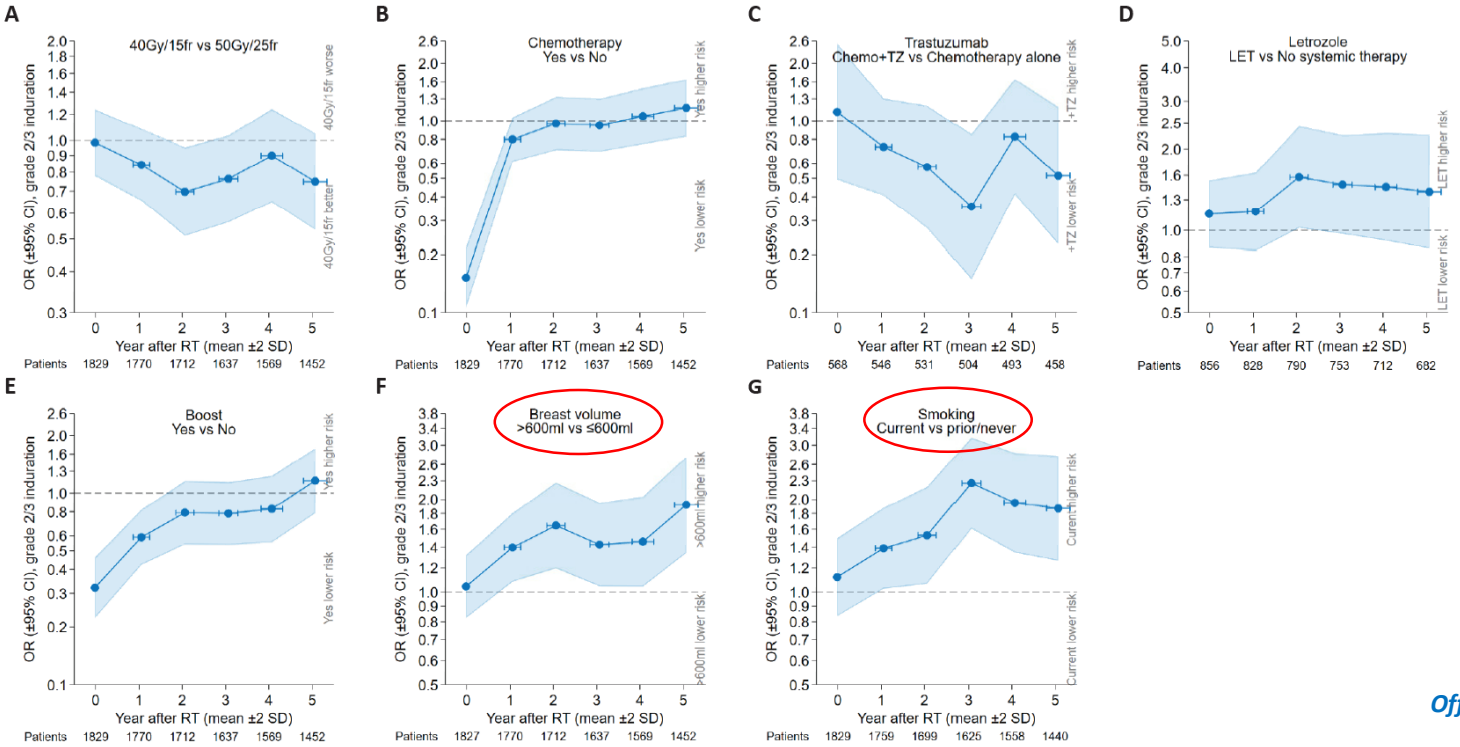
Fasthed – planlagte subgruppe analyser

Supplementary Figure 1. Odds ratio for grade 2 or 3 induration for fractionation (A), chemotherapy (B), Trastuzumab (C), Letrozole (D), boost (E), breast volume (F), smoking (G). Time of follow-up is defined by time after start of radiotherapy and defined as a given year if the time equals that year ± 6 months. Mean time for each year is potted with ± 2 standard deviations (SD).



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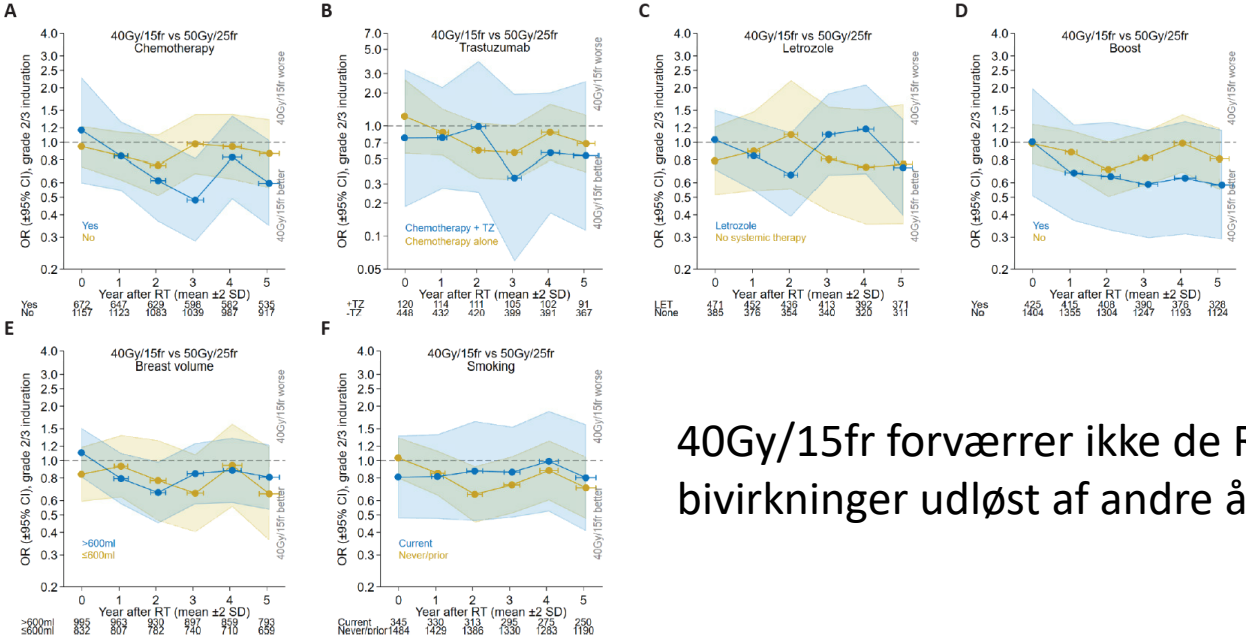
Fasthed i brystet – planlagte subgruppe analyser opgjort i forhold til antal behandlinger

Supplementary Figure 2. Odds ratio for grade 2 or 3 induration, 40Gy/15fr vs 50Gy/25fr depending on chemotherapy (A), Trastuzumab (B), Letrozole (C), boost (D), breast volume (E), smoking (F). Time of follow-up is defined by time after start of radiotherapy and defined as a given year if the time equals that year ± 6 months. Mean time for each year is potted with ± 2 standard deviations (SD).



40Gy/15fr forværrer ikke de RT-relaterede bivirkninger udløst af andre årsager

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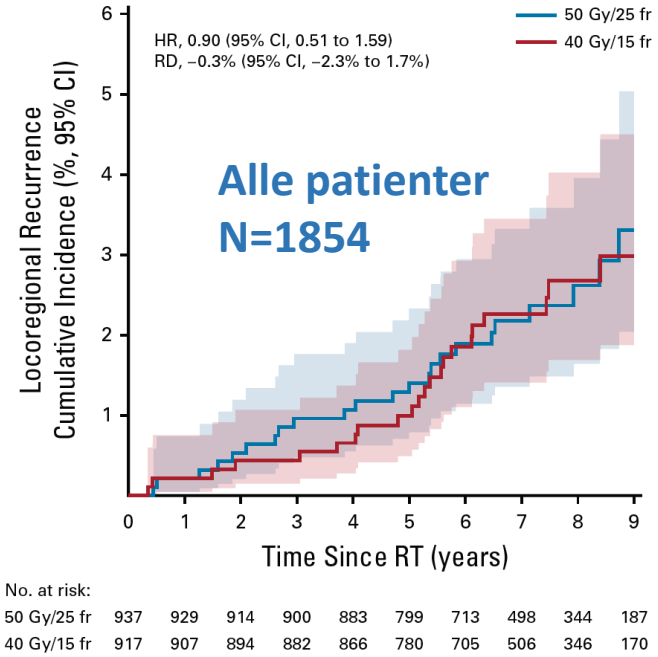
Loco-reg tilbagefald



LRR / antal patienter
50Gy: 19 / 814
40Gy: 14 / 794

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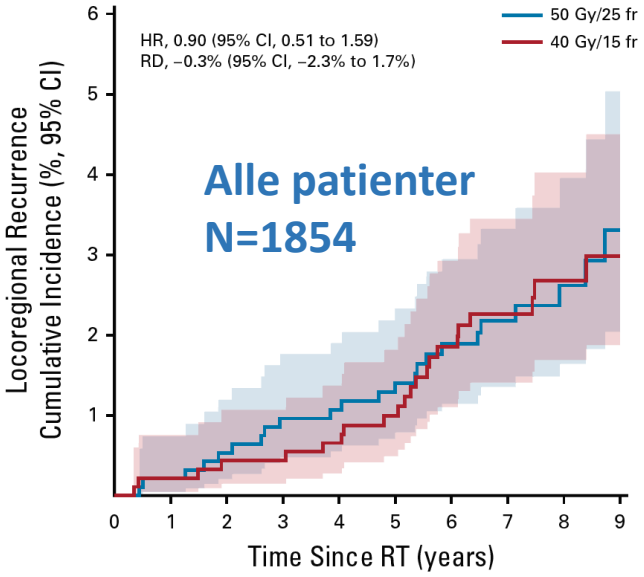
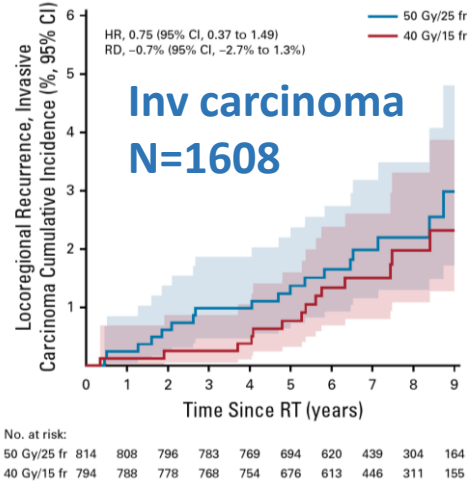
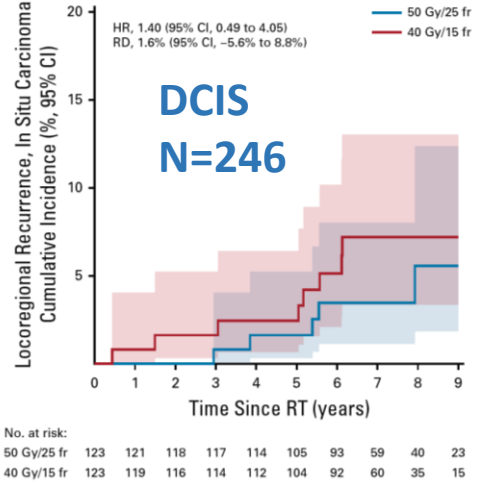
Loco-reg tilbagefald







LRR / antal patienter
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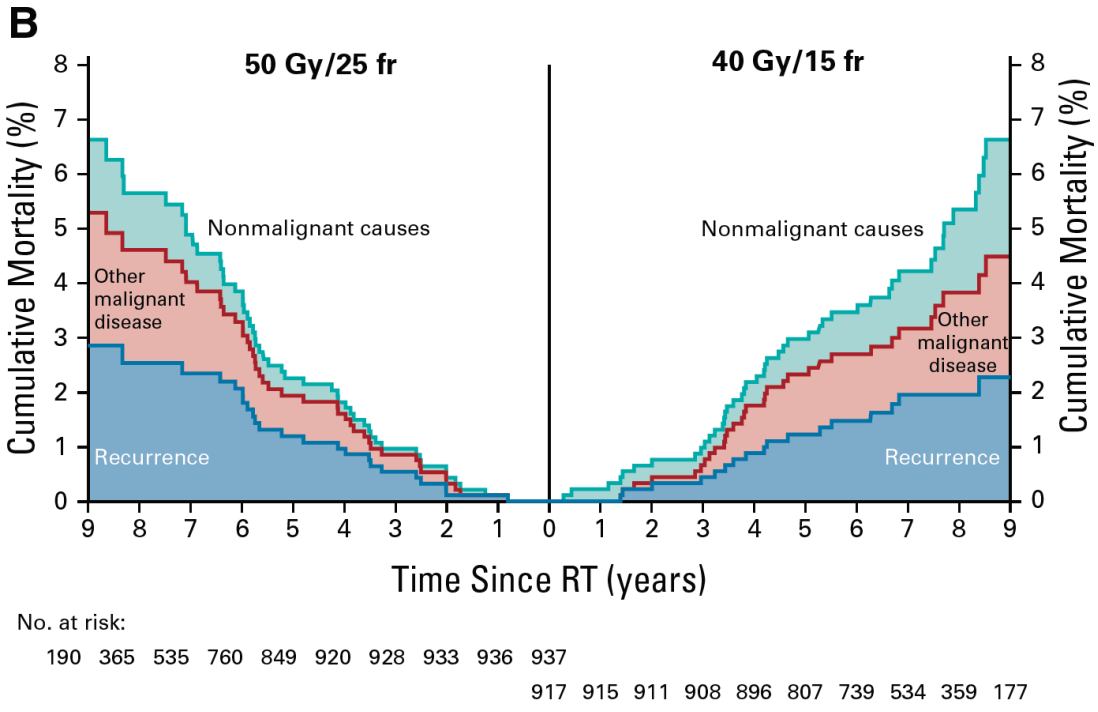
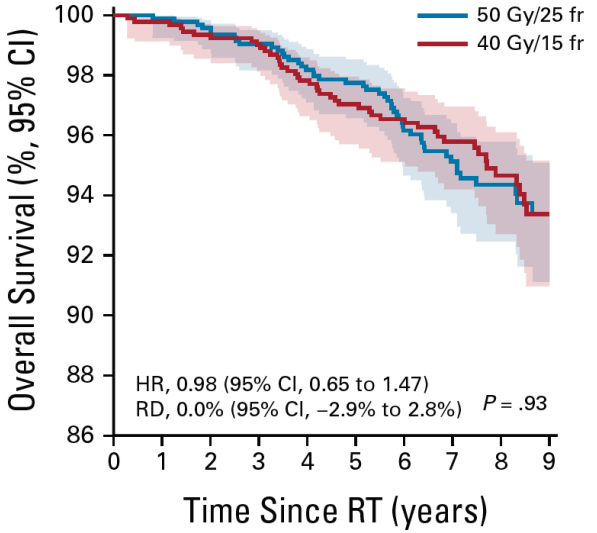
Overlevelse





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Konklusion

- 40 Gy / 15 fr øger ikke risikoen for fasthed, hverken i hele gruppen eller i de planlagte subgruppe analyser (boost, store bryster, kemoterapi og/eller rygere)

- Risikofaktorer for fasthed i brystet efter RT: stor bryststørrelse og aktuel ryger

- 40 Gy/15 fr er blevet testet i DBCG RT Skagen Trial 1, som inkluderede højrisiko brystkræftpatienter med indikation for lymfeknude bestråling, og de første resultater offentliggøres ved ESTRO 2022 på ca 3000 patienter

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Tak

- Tak til alle deltagende centre
- Tak til alle deltagende patienter
- Tak til Kræftens Bekæmpelse og CIRRO
- Tak til DBCG kontoret for hjælp og støtte

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