VUODEN TÄRKEÄT SÄDEHOITOTUTKIMUKSET

KYS

Jan Seppälä

Sädehoitopäivät
2015

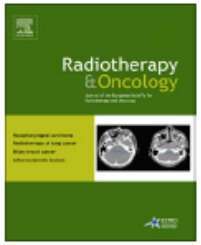
Viime vuoden tärkeät tapahtumat

- Adrian Begg (1946 – 2014), kuului mm. ESTROn säteilybiologia-toimikuntaan, piti kursseja kliinisestä säteilybiologiasta sekä kirjoitti säteilybiologiakolumnia ESTROn uutislehdessä.

Radiotherapy and Oncology 110 (2014) 562–563

Obituary

Adrian C. Begg



Radiotherapy and Oncology 86 (2008) 295–299
www.thegreenjournal.com

Editorial

Clinical radiobiology in 2008

Adrian Begg[a], Albert van der Kogel[b,*]

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Säteilybiologia ja hypofraktiointi

- Tässä luennossa tullaankin keskittymään tutkimuksiin, jotka liittyvät säteilybiologiaan ja erityisesti hypofraktiointiin.

Clinical Oncology 27 (2015) 260–269

Contents lists available at ScienceDirect

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Overview

The Radiobiology of Hypofractionation

Alan E. Nahum

Clatterbridge Cancer Centre, Bebington, UK

Eloonjäämisen mallintaminen, LQ-malli

- Solujen eloonjääminen (S) yhden fraktion jälkeen

$$S = e^{-(\alpha D + \beta D^2)}$$

ja eloonjääminen n-fraktion jälkeen ja josta on johdettu ns. biologisesti efektiivinen annos (BED)

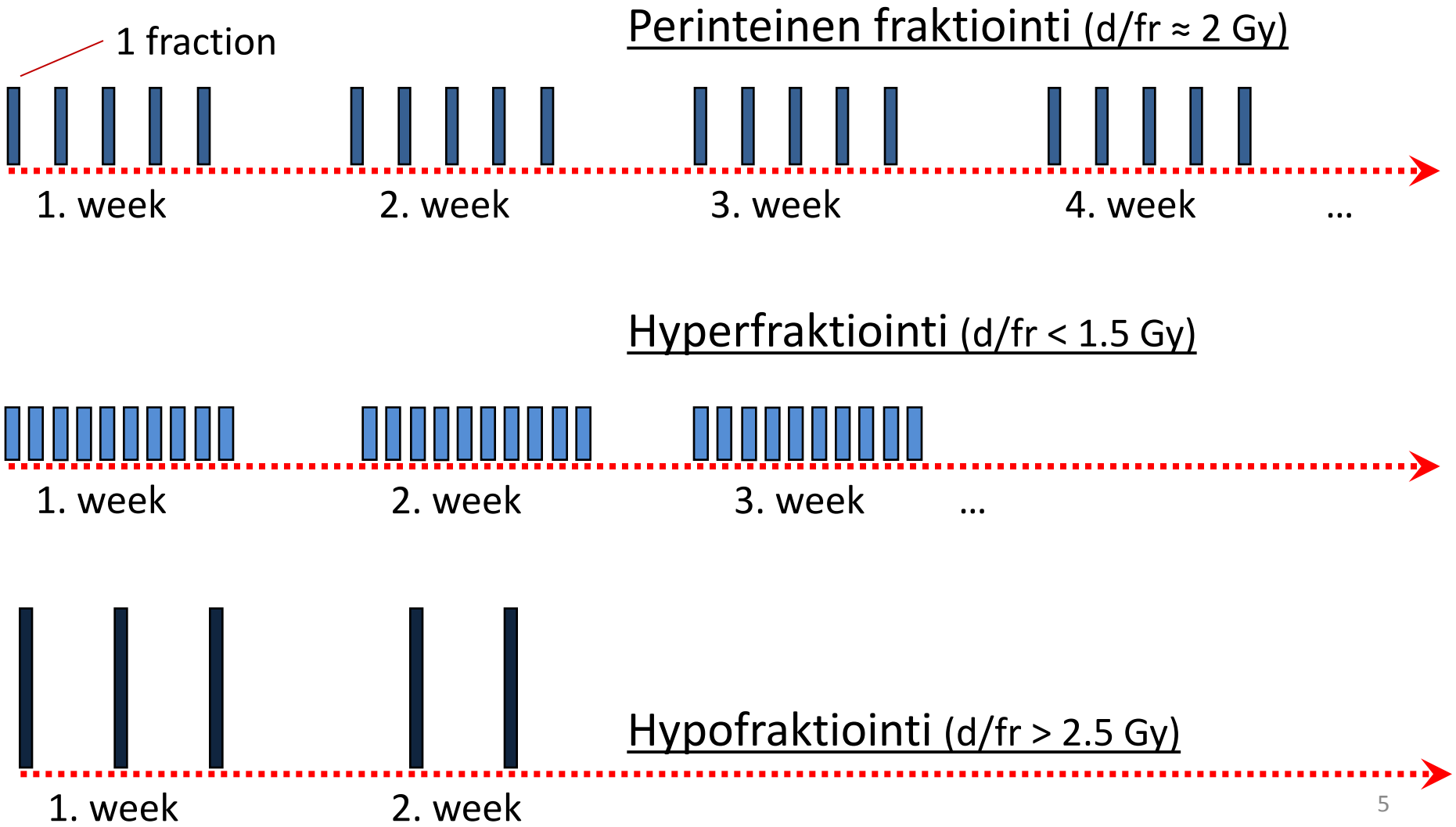
$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha / \beta}\right) - \frac{\ln 2}{\alpha T_p} T$$

Laskettuja BED arvoja voidaan käyttää hyväksi verrattaessa kahta eri fraktiointimallia keskenään, mm. ns. 2 Gy:n ekvivalenttiannoksen määritys

$$BED_1 = BED_2 \quad \Rightarrow \quad D_{2Gy} = D\left(\frac{d + \alpha / \beta}{2Gy + \alpha / \beta}\right)$$

Hypofraktiointi

Annos / fraktio (d/fr)



Hypofraktiointi ja TCP

- α/β –termin vaikutus solujen eloonjäämiseen eri fraktioinnilla.
- Tuumorikontrollin todennäköisyys (TCP) fraktiolukumäärän funktiona kun eri fraktiointimallit on normeerattu samaan normaalikudosvaurioon (NTCP) tuumorin eri α/β arvolla.
- Normaalikudokselle nyt α/β = 3 Gy ja tuumorille 1.5, 3.0, 5.0 ja 10 Gy.

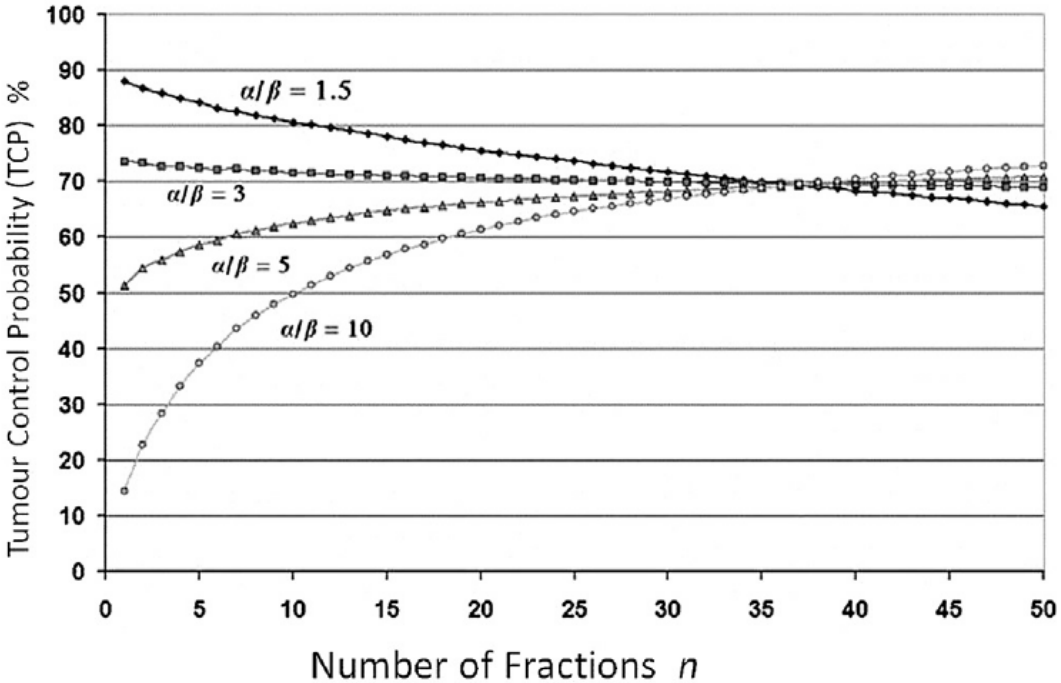


Fig 1. Tumour control probability (TCP) for a target volume (receiving a homogenous dose) over a range of fraction numbers (1–50) for different tumour α/β. All curves are for the same normal tissue complication probability (NTCP), i.e. 'isotoxic', here for rectal bleeding (4.3%) for which $\alpha/\beta = 3$ Gy has been used. Open circles, $\alpha/\beta = 10$ Gy; triangles, $\alpha/\beta = 5$ Gy; squares, $\alpha/\beta = 3$ Gy; diamonds, $\alpha/\beta = 1.5$ Gy (adapted from [7]).

Nahum, Clinical Oncology, 2015

Säteilybiologia ja hypofraktiointi

- Lineaari-neliöllinen fraktiointimalli (LQ-malli) näyttäisi olevan riittävän tarkka mallintamaan solujen eloonjäämistä myös erittäin korkeilla (>10Gy) kertafraktioilla.
- Onko tulevaisuudessa mahdollista optimoida jokaiselle potilaalle optimaalinen fraktiointimalli perustuen suunnitelman annosjakaumaan?

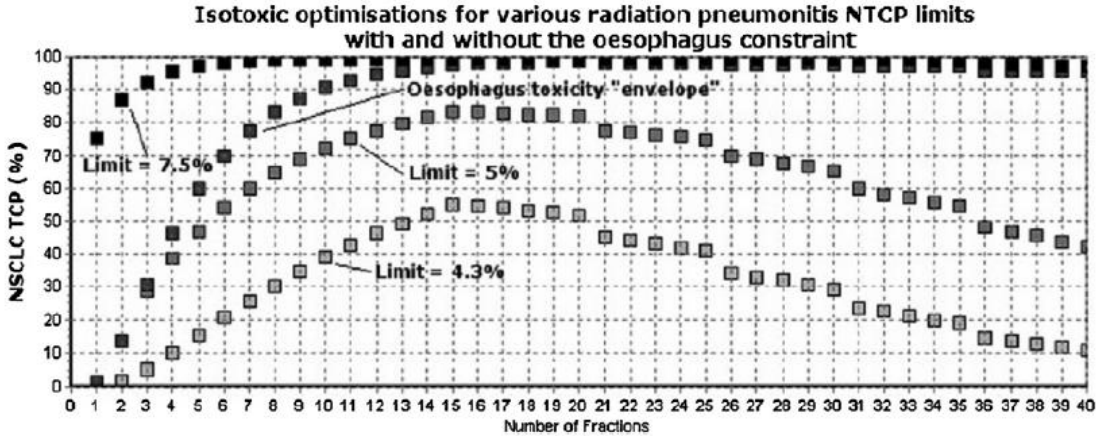


Fig 5. Tumour control probability (TCP) for a non-small cell lung cancer planning target volume of over a range of a number of fractions (1–40). Three different radiation pneumonitis normal tissue complication probability (NTCP) 'isotoxic' limits are shown: 4.3% (light grey), 5% (medium grey) and 7.5% (black). The oesophagus ('serial' organ) toxicity envelope (dark grey) is severely dose limiting for the 7.5% pneumonitis NTCP limit and 15 or fewer fractions. Reproduced with permission from [7].

Nahum, Clinical Oncology, 2015

Hypofraktiointi eturauhassyövän sädehoidossa

Katz and Kang *Radiation Oncology* 2014, **9**:1

RADIATION ONCOLOGY

Stereotactic body radiotherapy with or without external beam radiation as treatment for organ confined high-risk prostate carcinoma: a six year study

Abstract

Background: Stereotactic Body Radiotherapy (SBRT) has excellent control rates for low- and intermediate-risk prostate carcinoma.The role of SBRT for high-risk disease remains less studied. We present long-term results on a cohort of patients with NCCN-defined high-risk disease treated with SBRT.

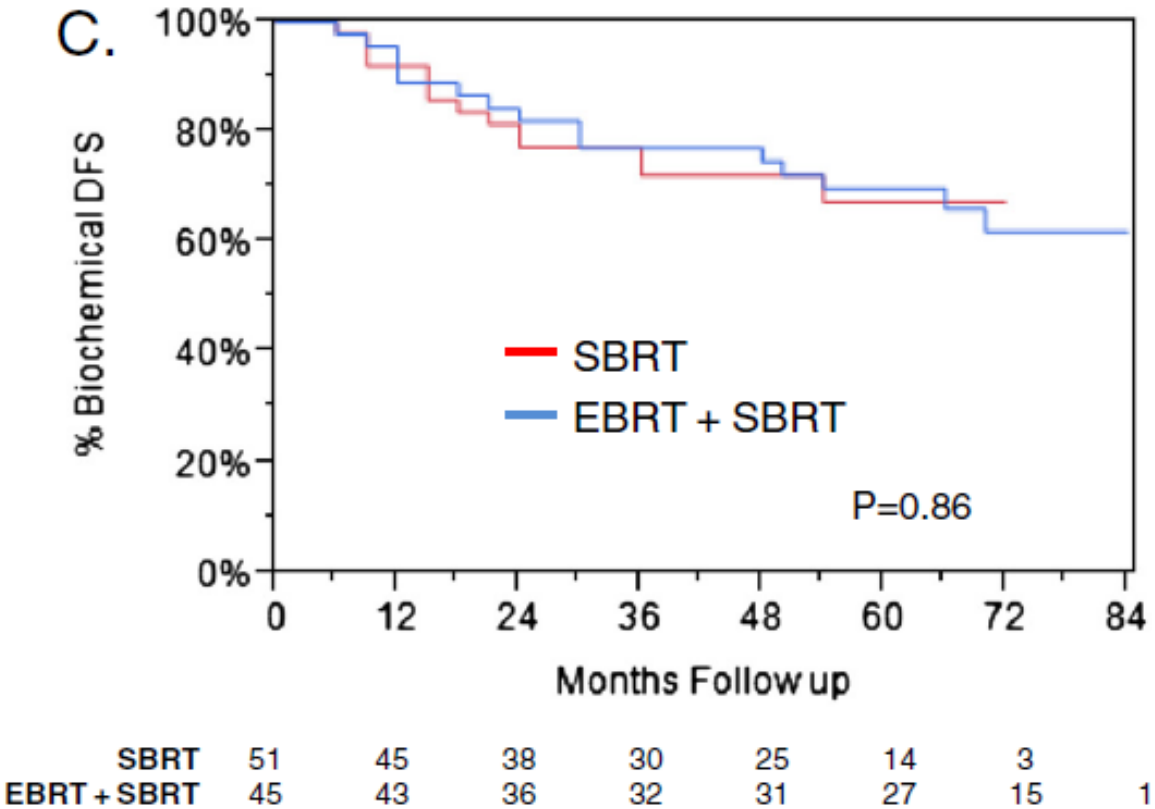
Methods: We retrospectively studied 97 patients treated as part of prospective trial from 2006–2010 with SBRT alone (n = 52) to dose of 35–36.25 Gy in 5 fractions, or pelvic radiation to 45 Gy followed by SBRT boost of 19–21 Gy in 3 fractions (n = 45). 46 patients received Androgen Deprivation Therapy. Quality of life and bladder/bowel toxicity was assessed using the Expanded Prostate Index Composite (EPIC) and RTOG toxicity scale.

Results: Median followup was 60 months. 6-year biochemical disease-free survival (bDFS) was 69%. On multivariate analysis, only PSA remained significant ($P < 0.01$) for bDFS. Overall toxicity was mild, with 5% Grade 2–3 urinary and 7% Grade 2 bowel toxicity. Use of pelvic radiotherapy was associated with significantly higher bowel toxicity ($P = .001$). EPIC scores declined for the first six months and then returned towards baseline.

Conclusions: SBRT appears to be a safe and effective treatment for high-risk prostate carcinoma. Our data suggests that SBRT alone may be the optimal approach. Further followup and additional studies is required to corroborate our results.

Keywords: Prostate cancer, Stereotactic radiotherapy, High-risk

Hypofraktiointi eturauhassyövän sädehoidossa



Katz and Kang, Radiat Oncol. 2014

- Biokemiallinen tautivapaa-aika korkean riskin eturauhassyöpäpotilaille (SBRT = 5 × 7 Gy ja EBRT+SBRT = 45 Gy + 3 × 7 Gy)

Hypofraktiointi eturauhassyövän sädehoidossa

- Miksi hypofraktiointia kannattaa siis käyttää eturauhassyövän sädehoidossa?
- Eturauhassyövällä on matalampi α/β –arvo kuin läheisillä kriittisillä normaaleilla kudoksilla (prostata ca α/β = 1.5 Gy kun esim. rektumin ja rakon myöhäiskomplikaatioille α/β = 3 Gy).
- Tällöin saavutetaan ns. terapeuttinen hyöty käyttämällä suuria kertafraktioita (ts. hypofraktiointia).

20 × 3 Gy ad 60 Gy		5 × 7 Gy ad 35 Gy	
PCa	Rektum	PCa	Rektum
Fraktiointi	Fraktiointi	Fraktiointi	Fraktiointi
n = 20 fr	n = 20 fr	n = 5 fr	n = 5 fr
d = 3 Gy/fr	d = 3 Gy/fr	d = 7 Gy/fr	d = 7 Gy/fr
α/β = 1,5 Gy	α/β = 3 Gy	α/β = 1,5 Gy	α/β = 3 Gy
D = 60 Gy	D = 60 Gy	D = 35 Gy	D = 35 Gy
2 Gy eq. dose ~ 77,1 Gy	**2 Gy eq. dose ~ 72 Gy**	**2 Gy eq. dose ~ 85 Gy**	**2 Gy eq. dose ~ 70 Gy**

Hypofraktiointi rintasyövän sädehoidossa

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss, John R Yarnold*, on behalf of the START Trialists' Group†*

Lancet Oncol 2013; 14: 1086–94

- **START-A:** 25 × 2Gy vs. 13 × 3 Gy (ad 39Gy) vs. 13 × 3.2 Gy (ad 41.6 Gy), all delivered in 5 weeks
- **START-B:** 25 × 2Gy vs. 15 × 2.67Gy (ad 40.05 Gy) in 3 weeks

Hypofraktiointi rintasyövän sädehoidossa

4·2–7·2; HR 0·77, 95% CI 0·51–1·16; p=0·21). In START-B, breast shrinkage, telangiectasia, and breast oedema were significantly less common normal tissue effects in the 40 Gy group than in the 50 Gy group.

	START-A				START-B		
	50 Gy (n=749)	41·6 Gy (n=750)	39 Gy (n=737)	Total (n=2236)	50 Gy (n=1105)	40 Gy (n=1110)	Total (n=2215)
Symptomatic rib fracture*							
Reported	5 (0·7%)	8 (1·1%)	9 (1·2%)	22 (1·0%)	17 (1·5%)	24 (2·2%)	41 (1·9%)
Confirmed†	0	0	1 (0·1%)	1 (<0·1%)	3 (0·3%)	3 (0·3%)	6 (0·3%)
Symptomatic lung fibrosis							
Reported	6 (0·8%)	9 (1·2%)	8 (1·1%)	23 (1·0%)	19 (1·7%)	19 (1·7%)	38 (1·7%)
Confirmed†	0	2 (0·3%)	1 (0·1%)	3 (0·1%)	2 (0·2%)	8 (0·7%)	10 (0·5%)
Ischaemic heart disease‡							
Reported	14 (1·9%)	11 (1·5%)	8 (1·1%)	33 (1·5%)	23 (2·1%)	17 (1·5%)	40 (1·8%)
Confirmed†							
Total	7 (0·9%)	5 (0·7%)	6 (0·8%)	18 (0·8%)	16 (1·4%)	8 (0·7%)	24 (1·1%)
Left sided	4 (0·5%)	1 (0·1%)	4 (0·5%)	9 (0·4%)	5 (0·5%)	4 (0·4%)	9 (0·4%)
Brachial plexopathy	0	1 (0·1%)	0	1 (<0·1%)	0	0	0

Data are n (%). *Reported cases include seven after trauma (five in START-A, two in START-B), and ten after metastases (five in START- A and five in START-B). †After imaging and further investigations. ‡26 patients in START-A and 22 in START-B had pre-existing heart disease at enrolment and were excluded.

Table 3: Incidence of other late adverse effects according to fractionation schedule

Breast Ca

Fraktiointi	
n =	15 fr
d =	2,67 Gy/fr
α/β =	3,5 Gy
D =	40,05 Gy

2 Gy eq. dose ~ 44,9 Gy

Plexus Brach.

Fraktiointi	
n =	15 fr
d =	2,67 Gy/fr
α/β =	3 Gy
D =	40,05 Gy

2 Gy eq. dose ~ 45,4 Gy

Plexus Brach. (worst case)

Fraktiointi	
n =	15 fr
d =	2,67 Gy/fr
α/β =	1 Gy
D =	40,05 Gy

2 Gy eq. dose ~ 49 Gy

Hypofraktiointi rintasyövän sädehoidossa

Acta Oncologica, 2009; 48: 822–831

informa healthcare

ORIGINAL ARTICLE

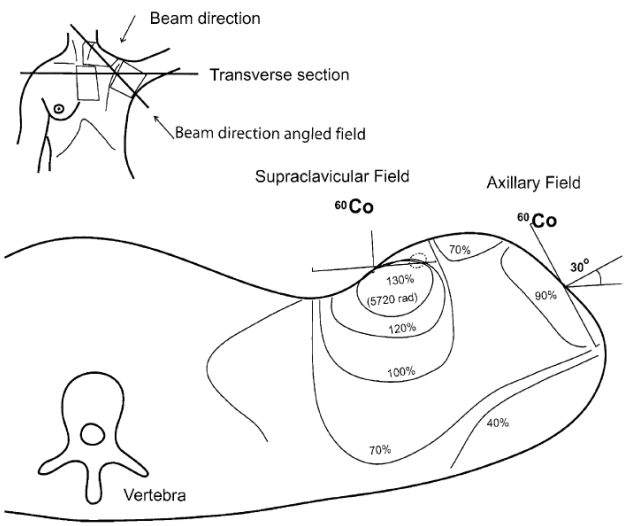
Hypofractionation in radiotherapy. An investigation of injured Swedish women, treated for cancer of the breast

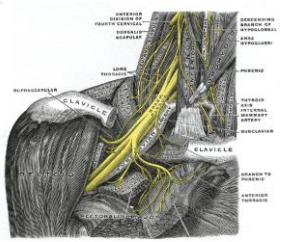
STEN FRIBERG[1] & BENGT-INGE RUDÉN[2]

[1]*Formerly at the Department of Oncology, Radiumhemmet, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden and* [2]*Division of Medical Radiation Physics, Department of Oncology-Pathology, Karolinska Institute and Stockholm University, Box 260, SE-171 76 Stockholm, Sweden*

Fraktiointi	
n =	10 fr
d =	4,5 Gy/fr
α/β =	3 Gy
D =	45 Gy
2 Gy eq. dose ~	**67,5 Gy**

Fraktiointi	
n =	13 fr
d =	6 Gy/fr
α/β =	3 Gy
D =	78 Gy
2 Gy eq. dose ~	**140 Gy**





The size of the individual fractions varied from 2.5 Gy 5 days per week to 6.0 Gy 2 days per week. Total absorbed dose varied from a biological equivalence of 45 to 146 Gy EQD_{2Gy} (6 Gy × 13). The highest

Hypofraktiointi ja sydänkuolleisuus?

Radiotherapy and Oncology 113 (2014) 73–78

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journal homepage: www.thegreenjournal.com

Cardiac toxicity

Long-term mortality from cardiac causes after adjuvant hypofractionated vs. conventional radiotherapy for localized left-sided breast cancer

Elisa K. Chan [a], Ryan Woods [b], Sean Virani [c], Caroline Speers [d], Elaine S. Wai [e], Alan Nichol [f], Mary L. McBride [b], Scott Tyldesley [f,*]

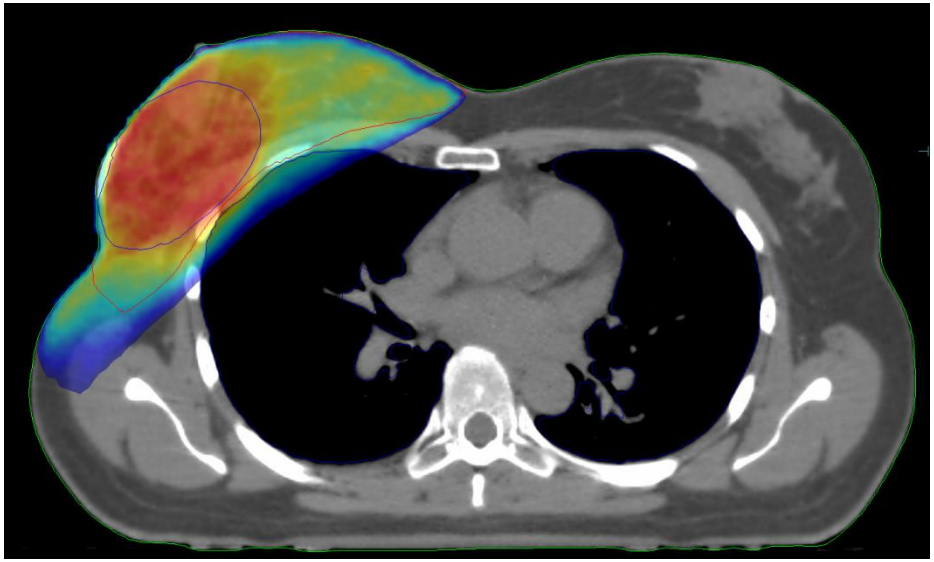
[a] *Department of Oncology, Saint John Regional Hospital;* [b] *BC Cancer Agency, Cancer Control Research Department, Vancouver;* [c] *Division of Cardiology, University of British Columbia, Vancouver;* [d] *BC Cancer Agency, Breast Cancer Outcomes Unit, Vancouver;* [e] *BC Cancer Agency, Radiation Therapy Program, Victoria; and* [f] *BC Cancer Agency, Radiation Therapy Program, Vancouver, Canada*

Conclusions: At 15-years follow-up, cardiac mortality is not statistically different among left-sided breast cancer patients treated with HF-WBI or CF-WBI.

SIB rintasyövän hypofraktioidussa sädehoidossa?

- Nykyiset sädehoidon toteutustekniikat mahdollistavat eri annostasojen samanaikaisen toteutuksen ja näin myös samanaikaisen booster-annoksen antamisen, ns. samanaikainen integroitu booster (SIB)
- Esimerkiksi: Koko rinta 16 × 2.5Gy ad 40.0 Gy,

  booster-alue 16 × 3 Gy ad 48.0 Gy



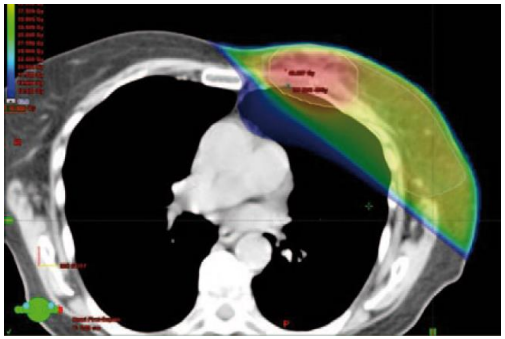
SIB rintasyövän hypofraktioidussa sädehoidossa?

Strahlenther Onkol 2014 · 190:646–653

Hypofractionation with simultaneous integrated boost for early breast cancer

Results of the German multicenter phase II trial (ARO-2010-01)

Kathrin Dellas[1,2] · Reinhard Vonthein[3,4] · Jörg Zimmer[5] · Stefan Dinges[6] · Alexander D. Boicev[7] · Peter Andreas[8] · Dorothea Fischer[9] · Cornelia Winkler[10] · Andreas Ziegler[3,4] · Jürgen Dunst[1,2,11] · ARO Study Group



Fraktiointi		
n =	16	fr
d =	3	Gy/fr
α/β =	3,5	Gy
D =	48	Gy
2 Gy eq. dose ~	**56,7**	**Gy**

Fraktiointi		
n =	16	fr
d =	2,5	Gy/fr
α/β =	3,5	Gy
D =	40	Gy
2 Gy eq. dose ~	**43,6**	**Gy**

- Potilaita 151
- Hoitoannokset: rinta 16 × 2.5 Gy ad 40.0 Gy, booster-alue 16 × 3 Gy ad 48.0 Gy

Conclusion

Hypofractionated radiotherapy with SIB after surgery for early stage breast cancer can be applied as planned while respecting dose constraints in all settings in all of Germany. It is experimental but warrants further investigation in randomized trials.

SIB rintasyövän sädehoidossa

Radiotherapy and Oncology 108 (2013) 269–272

Five year outcomes of hypofractionated simultaneous integrated boost irradiation in breast conserving therapy; patterns of recurrence

Enja J. Bantema-Joppe [a], Eline J. Vredeveld [a], Geertruida H. de Bock [b], Dianne M. Busz [a], Marleen Woltman-van Iersel [a], Wil V. Dolsma [a], Hans Paul van der Laan [a], Johannes A. Langendijk [a], John H. Maduro [a,*]

[a] Department of Radiation Oncology; and [b] Department of Epidemiology, University of Groningen, University Medical Center Groningen, The Netherlands

Patients and methods

From January 2005 to January 2008, 752 consecutive female invasive breast cancer patients (stages I–III) were treated with 3D-CRT-SIB as part of BCT at the department of Radiation Oncology of the University Medical Center Groningen [2]. Patients were irradiated with 28 fractions of 1.8 Gy to the whole breast and 2.3 Gy (76%) or 2.4 Gy (in case of focal irradicality) to the surgical bed.

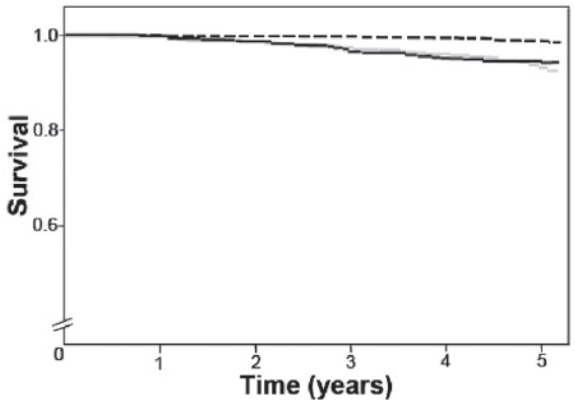
Fraktiointi	
n =	28 fr
d =	1,8 Gy/fr
α/β =	3,4 Gy
D =	50,4 Gy
2 Gy eq. dose ~	**48,5 Gy**

Fraktiointi	
n =	28 fr
d =	2,3 Gy/fr
α/β =	3,4 Gy
D =	64,4 Gy
2 Gy eq. dose ~	**68 Gy**

SIB rintasyövän sädehoidossa

more detail by van der Laan et al. [1]. Advantages of the 3D-CRT-SIB compared to the conventional sequential boost technique are increased dose homogeneity with less unintended excessive dose outside the boost area, in combination with a higher dose per fraction to the tumour bed, resulting in a shorter overall treatment time [1]. Previously, we reported the 3-year outcomes, with a local

In conclusion, the use of hypofractionated 3D-CRT-SIB as part of breast conserving therapy results in excellent 5-year local control rates.



Number at risk

	0y	1y	2y	3y	4y	5y	5-year % (95% CI)
LC	752	747	733	707	659	376	98.9 (98.1-99.7)
DMFS	752	744	726	695	645	369	94.2 (92.4-96.0)
OS	752	747	738	687	589	380	93.3 (91.3-95.3)

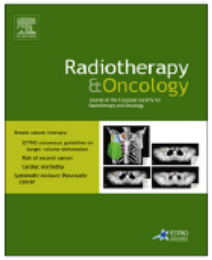
Fig. 1. Kaplan–Meier curves with actuarial 5-year local control (LC) (dotted line), distant metastases free-survival (DMFS) (black), and overall survival (OS) (grey) (with corresponding 95% confidence intervals (CI)), including number at risk.

Rintasyövän sädehoito, kohteen rajaaminen

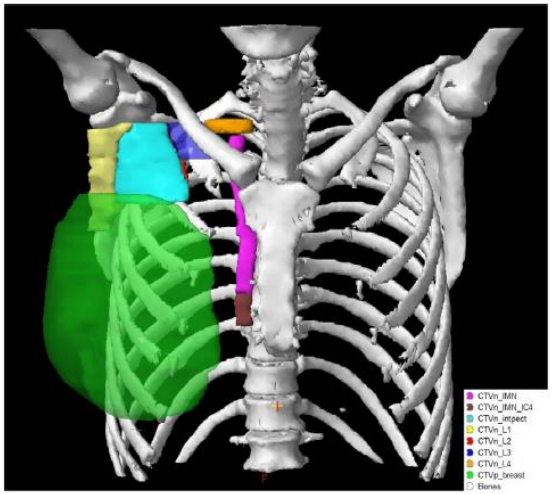
Radiotherapy and Oncology 114 (2015) 3–10

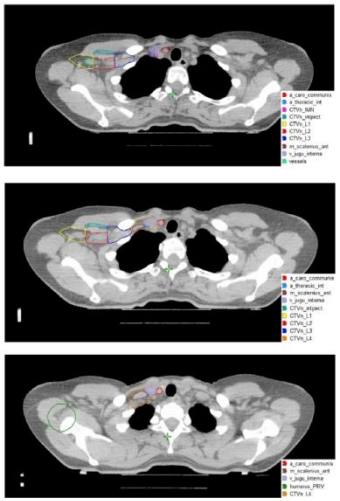
ESTRO consensus guidelines

ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer



Birgitte V. Offersen [a,*], Liesbeth J. Boersma [b], Carine Kirkove [c], Sandra Hol [d], Marianne C. Aznar
Albert Biete Sola [f], Youlia M. Kirova [g], Jean-Philippe Pignol [h], Vincent Remouchamps [i],
Karolien Verhoeven [j], Caroline Weltens [j], Meritxell Arenas [k], Dorota Gabrys [l], Neil Kopek [m],
Mechthild Krause [n], Dan Lundstedt [o], Tanja Marinko [p], Angel Montero [q], John Yarnold [r], Philip Poortmans [s]





"Currently, target volume delineation can be considered as the weakest part of the quality chain in RT."

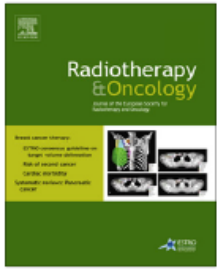
"The goal with this ESTRO consensus is to provide a useful and reproducible guideline for target volume delineation for RT for early breast cancer."

Rintasyövän sädehoito, kohteen rajaaminen

Guidelines

Radiotherapy and Oncology 114 (2015) 11–16

Vessel based delineation guidelines for the elective lymph node regions in breast cancer radiation therapy – PROCAB guidelines



Karolien Verhoeven [a,*], Caroline Weltens [a], Vincent Remouchamps [b], Khalil Mahjoubi [b], Liv Veldeman [c], Benoit Lengele [d], Eszter Hortobagyi [a], Carine Kirkove [d]

[a] University Hospitals Leuven/KU Leuven; [b] Clinique Sainte Elisabeth (AMPR), Namur; [c] Ghent University Hospital; and [d] Catholic University of Louvain, Brussels, Belgium

Conclusion: With this project a national as well as a European (ESTRO) consensus guideline for the delineation of the regional lymph node areas in breast RT is reached. The new delineation atlas is vessel-based and no longer field-based.

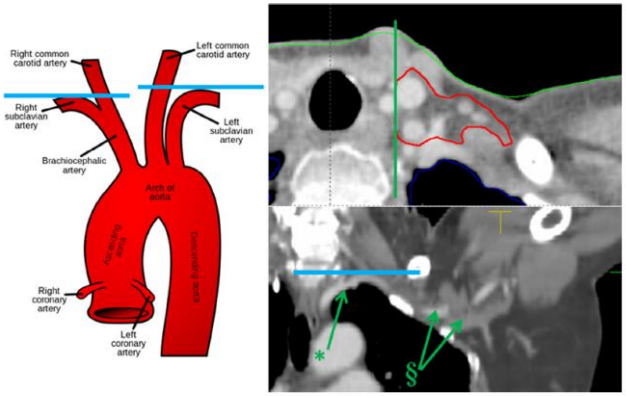


Fig. 2. The cranial border of level 4 or the supraclavicular region. *Subclavian artery arch. §Axillary artery and vein.

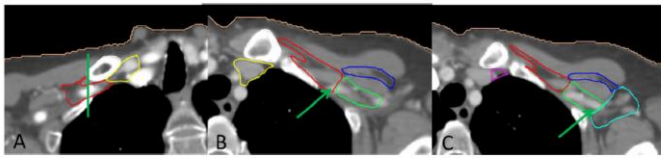


Fig. 3. Cranial border of level 3 (A), level 2 (B) and level 1 (C) of the axilla.

"These new guidelines are introduced because there is an urgent need to update the existing guidelines and especially to reach a consensus."

"… the target volume is concentrated 5 mm around the veins and is not defined by muscles and bony structures."

Yhteenveto

- Säteilybiologian mallintaminen on kehittynyt paljon viimeisten vuosikymmenien aikana.
- LQ-malli näyttäisi kliinisten tulosten perusteella ennustavan hyvin eri fraktiointimallien biologisen tehon (myös hypofraktioinnissa) ja mallia käyttämällä voidaan välttää suuret virheet potilaiden sädehoitoannosten suunnittelussa.
- Hypofraktioinnilla on selkeästi vankka tulevaisuus sädehoidossa.
- Sädehoidon nykytekniikoilla kriittisiä elimiä voidaan väistää entistä tehokkaammin, jolloin hypofraktiointia voidaan käyttää myös suunnitellusti syövissä joilla on korkeampi α/β kuin viereisillä kudoksilla.
- Fraktiointien lomassa tulee myös muistaa, että kaikki alkaa hoitokohteen rajaamisesta.

Kiitos tarkkaavaisuudestanne!

"The possible combinations in clinical radiation therapy of daily dose, total dose and interval from the first treatment to the last, are, in principle, infinite, and, in practice, finite but too numerous to count"

James D. Cox, 1985