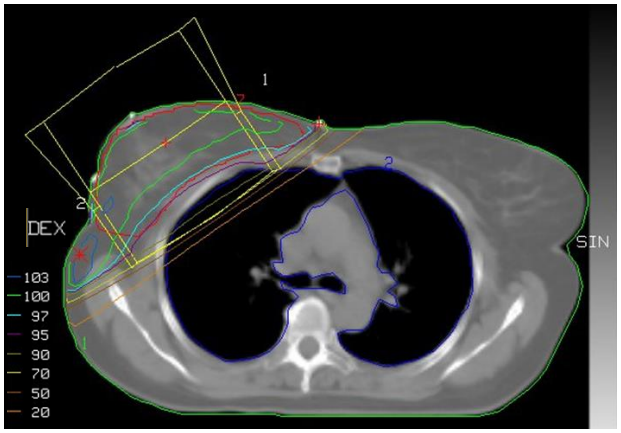
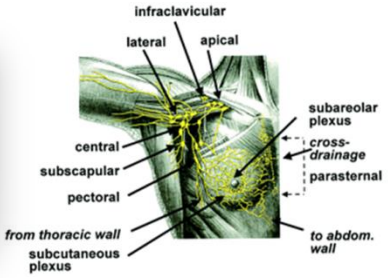
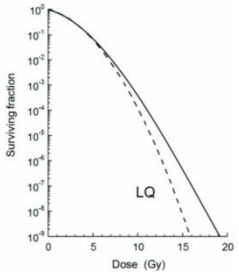
Onko hypofraktiointi uusi standardi?



Heikki Minn, professori, ylilääkäri
Syöpäklinikka/TO6E

TYKS
TURUN YLIOPISTOLLINEN KESKUSSAIRAALA
TURKU UNIVERSITY HOSPITAL

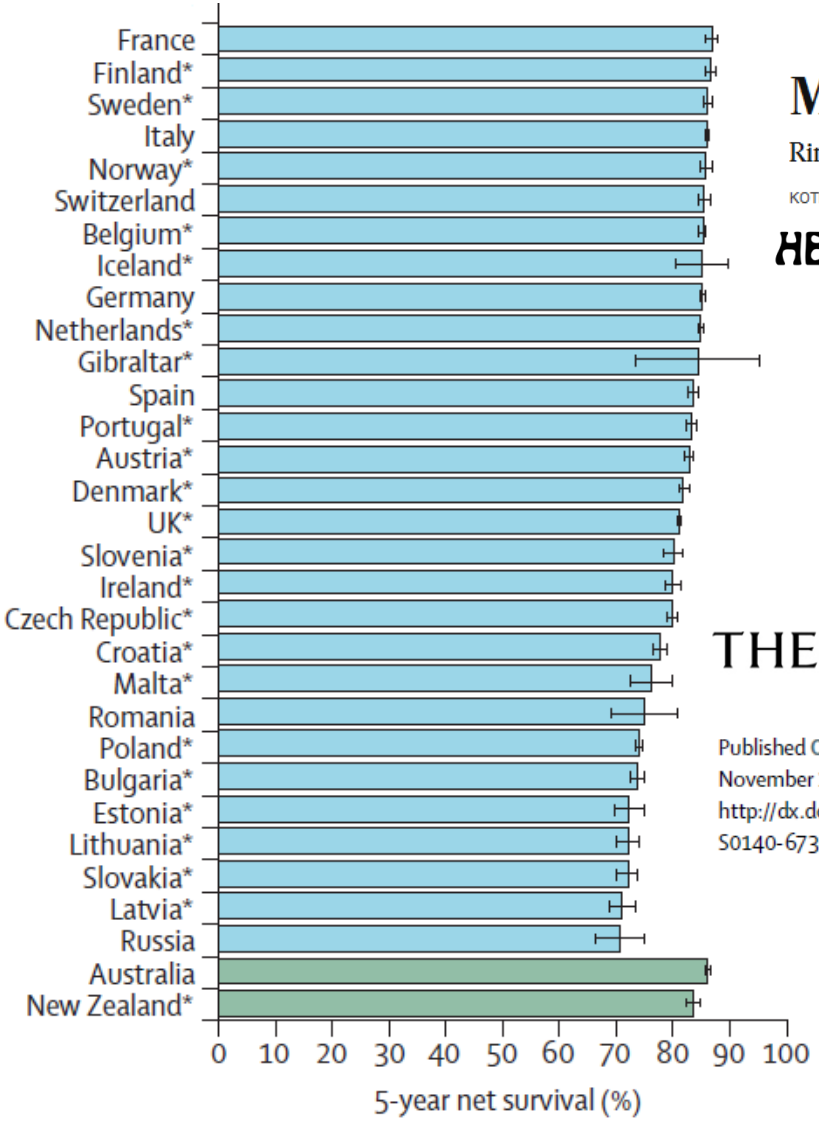




Luennon sisältö (15 +5 min)

- Mitkä tutkimukset ovat johtaneet nykyiseen käytäntöön?
- Tämänhetkiset suositukset: NICE/ASTRO/ESMO
- Pitkäaikaisseurantaan (> 10v) perustuvat tulokset (START A/B)
- Turun kokemukset 2010-2014
- Tulevaisuus

Rintasyövän ennuste Euroopassa 2005-2009
Concord-2 tutkimus: globaalinen aineisto



Moni syöpä paranee Suomessa kokonaan

Rintasyövän hoitotulokset ovat maailman huippua, vertailu havaitsi

KOTIMAA 27.11.2014 2:00

HELSINGIN SANOMAT

THE LANCET

Published Online
November 26, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)62038-9

Fakta

Hoitotulokset kohenevat

- Rintasyövästä selviää Suomessa lähes 87 prosenttia sairastuneista.
- Eturauhassyövän saaneista paranee 93 prosenttia.
- Leukemiaan sairastuneista aikuisista paranee joka toinen ja lapsista 82 prosenttia.
- Kohdunkaulansyöpään sairastuneista paranee 65 prosenttia.
- Suoliston syövistä (paksusuoli ja peräsuoli) selviää 63 prosenttia.
- Munasarjasyöpään sairastuneita paranee 45 prosenttia.
- Keuhkosyöpään sairastuneista paranee 12 prosenttia, maksasyövän saaneista 8 prosenttia.

Neljä kattavaa satunnaistettua tutkimusta

Trials of hypofractionated WBI versus conventional fractionation in early stage breast cancer.

Trial	Years conducted	#	Fractionation Gy/# of fractions	Boost (%)	Local recurrence (%)	Time point
RMH/GOC) [15] and [16]	1986–1998	470	50/25	74	12.1	10 years
		466	42.9/13	75	9.6	
		474	39/13	74	14.8	
START A [17]	1998–2002	749	50/25	60	3.6	5 Years
		750	41.6/13	61	3.5	
		737	39/13	61	5.2	
START B [18]	1999–2001	1105	50/25	41	3.3	5 Years
		1110	40/15	44	2.2	
OCOG [21]	1993–1996	612	50/25	0	6.7	10 Years
		622	42.5/16	0	6.2	

RMH/GOC: Royal Marsden Hospital, Sutton and Gloucestershire Oncology Centre; START: Standardization of Breast Radiotherapy; OCOG: Ontario Clinical Oncology Group.

Freedman ym. *Radiother Oncol* 2013;106:15-20

NICE National Institute for Health and Care Excellence

2009

Early and locally advanced breast cancer

Radiotherapy

Radiotherapy (breast) for patients with early invasive breast cancer

After breast conserving surgery: Patients should have breast radiotherapy.

After breast conserving surgery or mastectomy: Use external beam radiotherapy, giving 40 Gy in 15 fractions as standard practice.

After breast conserving surgery and breast radiotherapy, at high risk of local recurrence: Offer external beam boost to the site of local excision. Inform patients that cosmesis is likely to be worse, particularly in women with larger breasts.

http://pathways.nice.org.uk/pathways/early-and-locally-advanced-breast-cancer#path=view%3A/pathways/early-and-locally-advanced-breast-cancer/early-and-locally-advanced-breast-cancer-adjuvant-therapy.xml&content=view-node%3Anodes-radiotherapy

FRACTIONATION FOR WHOLE BREAST IRRADIATION: AN AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) EVIDENCE-BASED GUIDELINE

ASTRO TARGETING CANCER CARE

Table 1. Evidence supports the equivalence of hypofractionated whole breast irradiation with conventionally fractionated whole breast irradiation for patients who satisfy all of these criteria*

1. Patient is 50 years or older at diagnosis.
2. Pathologic stage is T1–2 N0 and patient has been treated with breast- conserving surgery.
3. Patient has not been treated with systemic chemotherapy.
4. Within the breast along the central axis, the minimum dose is no less than 93% and maximum dose is no greater than 107% of the prescription dose (±7%;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

* For patients who do not satisfy all of these criteria, the task force could not reach consensus and therefore chose not to render a recommendation either for or against hypofractionated whole breast irradiation in this setting. Please see the text for a thorough discussion of tumor grade. Patients receiving any type of whole breast irradiation should generally be suitable for breast-conserving therapy with regards to standard selection rules (*e.g.*, not pregnant, no evidence of multicentric disease, no prior radiotherapy to the breast, no history of certain collagen-vascular diseases).

The recommendations contained herein will expire on December 31, 2015. The ASTRO Guidelines Subcommittee will monitor this guideline and initiate an update when so indicated.

Smith ym. *Int J Radiat Oncol Biol Phys* 2011;81:59-68

International Journal of Radiation Oncology Biology Physics
Official Journal of the American Society for Radiation Oncology ASTRO

Annals of Oncology 24 (Supplement 6): vi7–vi23, 2013
doi:10.1093/annonc/mdt284
Published online 22 August 2013

Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

E. Senkus[1], S. Kyriakides[2], F. Penault-Llorca[3,4], P. Poortmans[5], A. Thompson[6], S. Zackrisson[7] & F. Cardoso[8,9], on behalf of the ESMO Guidelines Working Group*

[1]*Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland;* [2]*Europa Donna Cyprus, Nicosia, Cyprus;* [3]*Department of Pathology, Centre Jean Perrin, Clermont-Ferrand;* [4]*EA 4677 Université d'Auvergne, Clermont-Ferrand, France;* [5]*Institute Verbeeten, Tilburg, The Netherlands;* [6]*Dundee Cancer Centre, University of Dundee, Dundee, UK;* [7]*Diagnostic Radiology, Lund University, Malmö, Sweden;* [8]*European School of Oncology, Milan, Italy;* [9]*Breast Cancer Unit, Champalimaud Centre Center, Lisbon, Portugal*

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

Published on behalf of

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

European Society for Medical Oncology

RT doses and fractionation: Doses used for local and/or regional adjuvant irradiation have traditionally been 45–50 Gy in 25–28 fractions of 1.8–2.0 Gy with a typical boost dose of 10–16 Gy in 2 Gy single doses. Shorter fractionation schemes (e.g. 15–16 fractions with 2.5–2.67 Gy single dose) have shown similar effectiveness and comparable side-effects [I, A] [50–52]. Strictly speaking, these data are not fully validated in young patients and in patients with mastectomy and/or additional regional irradiation, as these patients were either not included or underrepresented in the relevant trials. As hypofractionation in many places is being introduced for all patient subgroups, and in the unlikelihood of prospective, randomised trials that will test this, we advise to carefully monitor, evaluate and compare outcomes in those patients. Further hypofractionation (to five fractions) is currently the subject of trials.

ASTRO releases list of five radiation oncology treatments to question as part of national Choosing Wisely® campaign

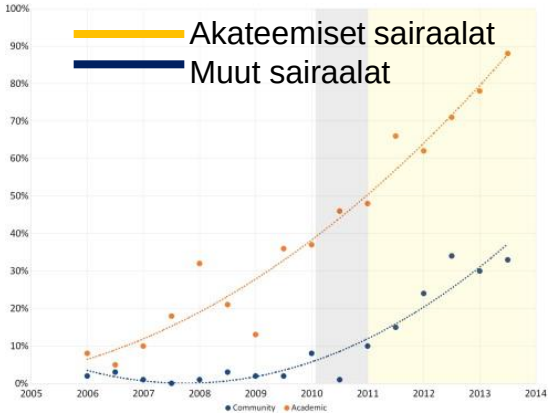
Atlanta, September 23, 2013

Choosing Wisely®

An initiative of the ABIM Foundation

ASTRO's five recommendations are:

- Don't initiate whole breast radiotherapy as a part of breast conservation therapy in women age ≥50 with early stage invasive breast cancer without considering shorter treatment schedules.
  Whole breast radiotherapy decreases local recurrence and improves survival of women with invasive breast cancer treated with breast conservation therapy. Most studies have utilized "conventionally fractionated" schedules that deliver therapy over 5-6 weeks, often followed by 1-2 weeks of boost therapy. Recent studies, however, have demonstrated equivalent tumor control and cosmetic outcome in specific patient populations with shorter courses of therapy (approximately 4 weeks). Patients and their physicians should review these options to determine the most appropriate course of therapy.



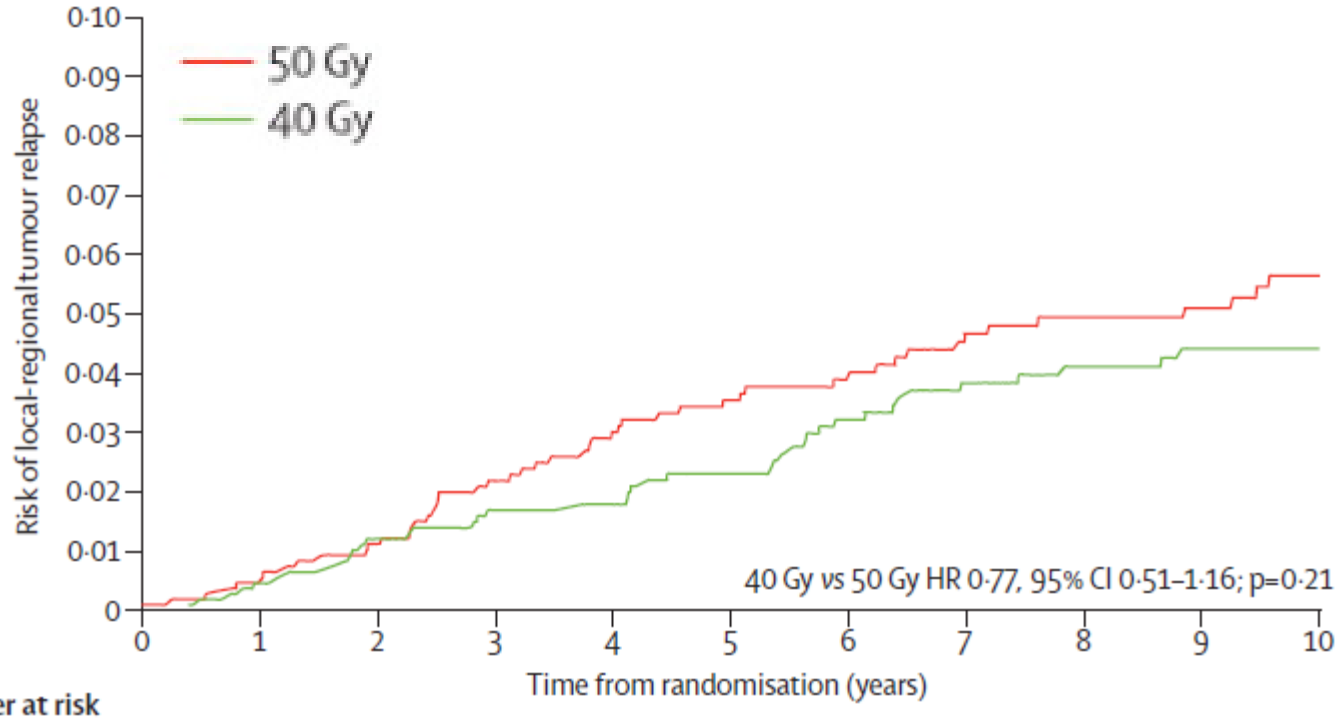
Hypofraktiointi USA:ssa
> 70 v naisilla

Rajagopalan ym.
pro practical radiation oncology 2015;5:63-69

ASTRO TARGETING CANCER CARE

https://www.astro.org/news-and-media/news-releases/2013/astro-releases-list-of-five-radiation-oncology-treatments-to-question.aspx

Kumulatiivinen paikallisten uusiutumien riski START-B tutkimuksessa

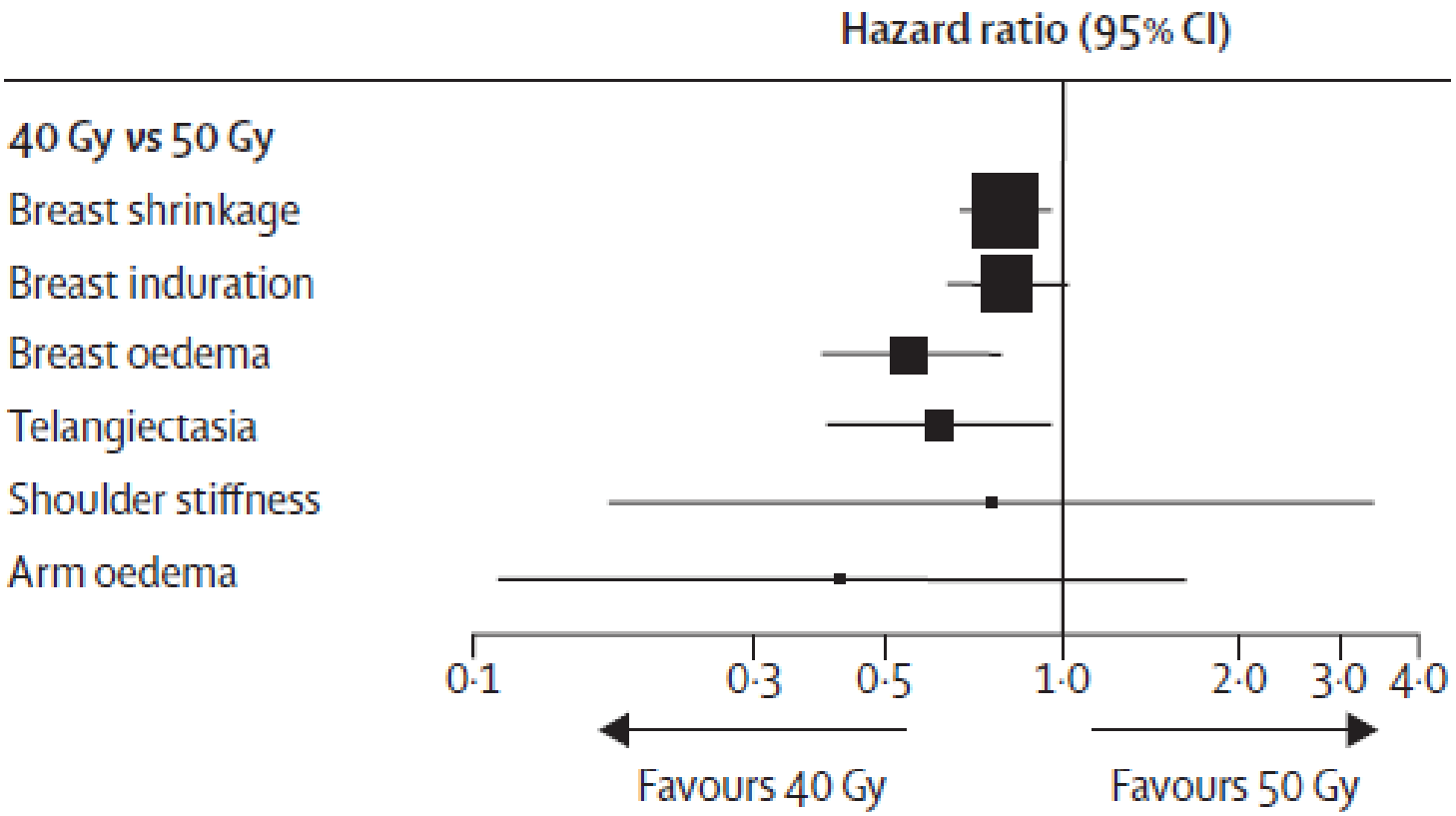


Number at risk

50 Gy	1105	1077	1047	1002	952	893	816	749	688	620	388
40 Gy	1110	1085	1055	1016	982	927	843	772	710	639	412

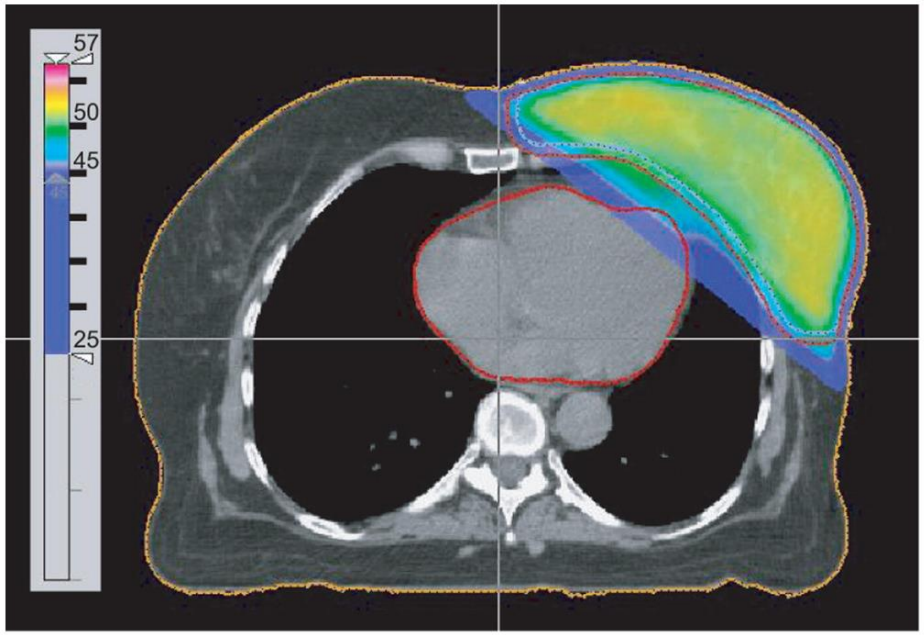
Haviland ym. THE LANCET Oncology 2013;1086-1094

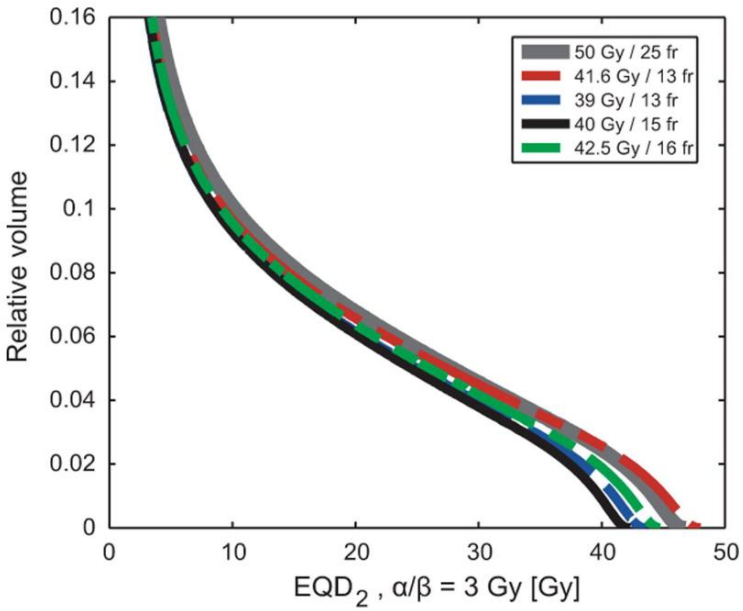
Normaalikudoskomplikaatioiden riski START-B tutkimuksessa



Haviland ym. THE LANCET Oncology 2013;1086-1094

Hypofraktioinnin sydänvaikutukset?





α/ß (Gy)	2.0 Gy ekvivalenttiannos 50Gy/25F	42.5Gy/16F	40Gy/15F
3.0	50.0	48.5	45.5
1.5	50.0	51.0	48.0

Appelt ym.
Clin Oncol 2013;25:147-152

Yarnold J. ASTRO 2014

län, kirurgian, kainalolevinneisyyden, erilaistumisasteen, boosterin ja solunsalpaajien käytön vaikutus paikallisiin uusiutumiin

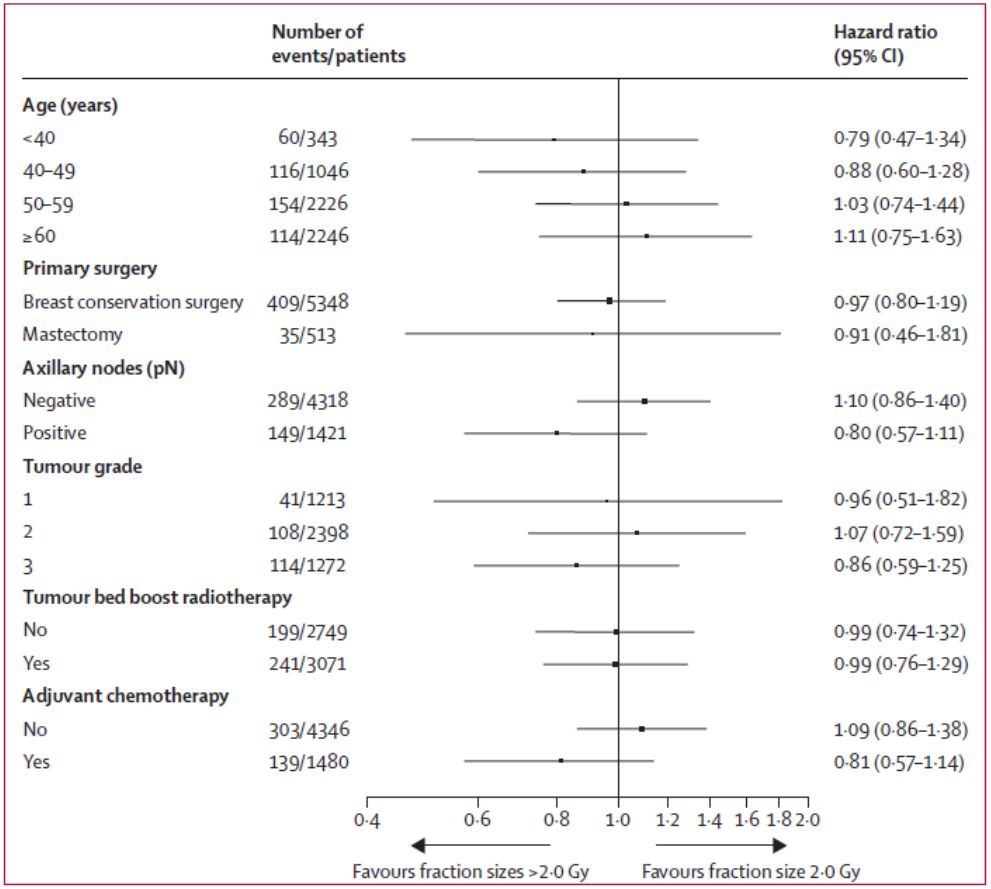
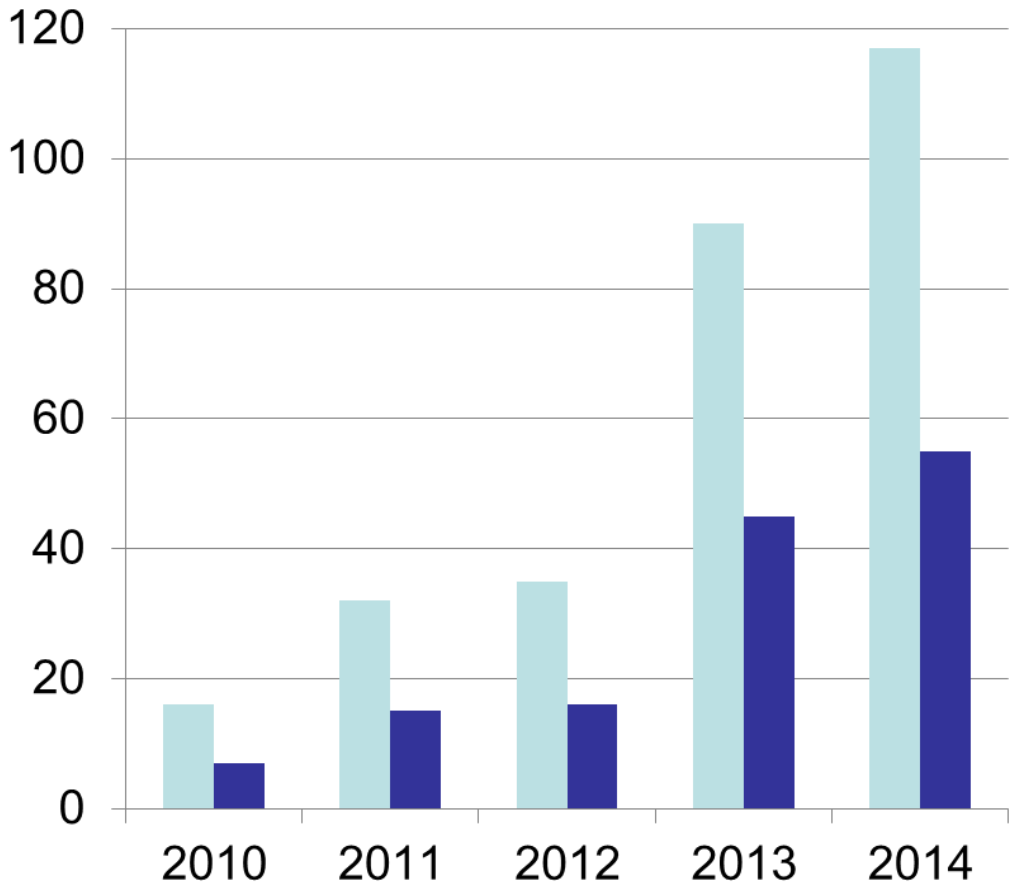


Figure 4: Meta-analysis of local-regional relapse comparing hypofractionated regimens versus 50 Gy in 25 fractions
Includes 5861 patients from the START pilot trial, START-A, and START-B.

Haviland ym. THE LANCET Oncology 2013;1086-1094

Hypofraktioidut kainalonegatiivisen rinnan sädehoidot TYKS syöpäklinikalla

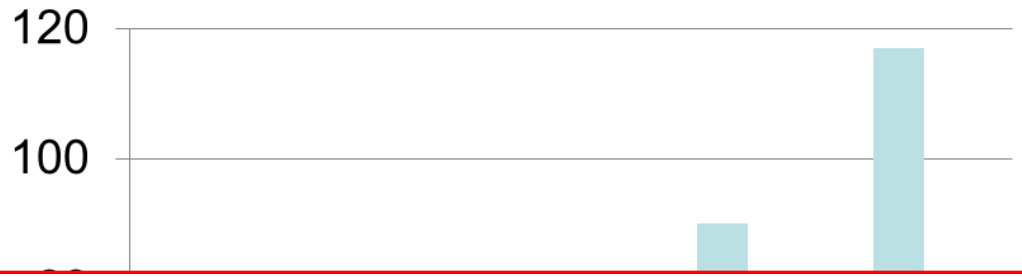


Potilasta/v

Osuus (%) N0-rinnoista

2014 yli puolet potilaista sai hypofraktioidun sädehoidon!

Hypofraktioidut kainalonegatiivisen rinnan sädehoidot TYKS syöpäklinikalla



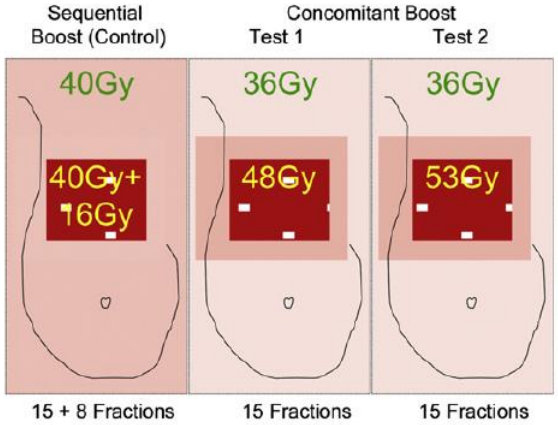
Hypofraktioitu sädehoito

Hypofraktioitu sädehoito 16 x 2.66 Gy ad 42.5 Gy voidaan antaa rintaan säästävästi leikatuille potilaille, joilla annosjakauma on tasainen (100 ± 7 %) ja rinnan koko ei ole hyvin suuri jos kyseessä on T1-2N0 yksittäinen tuumori ja kasvain on leikattu puhtain marginaalein (>2 -3mm). Nuori ikä ei ole osoittautunut esteeksi hoitaa hypofraktioidusti, laajemmat aineistot kuitenkin puuttuvat. Hypofraktioidussa hoidossa voidaan käyttää 10-16 Gy tehosteannosta tarpeen mukaan. Sydänannos on pidettävä mahdollisimman pienenä.

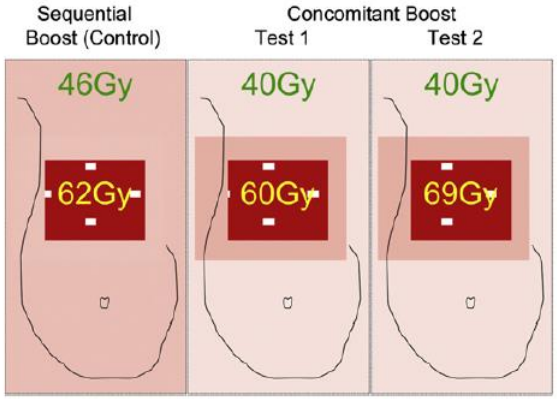
Tulevaisuus

UK IMPORT HIGH trial testing synchronous tumour bed boost

c) Prescribed total doses delivered in 23 fractions (Control group) or 15 fractions (Test groups)



d) Total doses delivered as if in 2.0Gy fractions, assuming $\alpha/\beta = 3.0$Gy



FAST Forward Trial: Whole Breast or Chest Wall (n=4000)

Trial group	Fraction size	Total dose (Gy)	Fractions (N)	Time (weeks)
Control	2.67	40	15	3
*Test 1	5.4	27	5	1
Test 2	5.2	26	5	1

*Iso-effective with Control assuming $\alpha/\beta=3$Gy

John Yarnold. ASTRO 2014

Yarnold ym. *Int J Radiat Oncol Biol Phys* 2011;79:1-9
Bentzen ja Arnold. *Clin Oncol* 2014;26:599-601

Yhteenveto

- Suurin osa säästävästi leikatuista varhaisvaiheen (N0) rintasyövistä voidaan hoitaa hypofraktioidulla tekniikalla
- Näyttöön perustuva lääketiede viittaa siihen, että sekä paikallinen kontrolli että kosmeesi ovat yhtä hyviä tai jopa parempia kuin perinteisellä fraktioinnilla
- Näyttö ei ole kattava tiettyjen alaryhmien (hyvin nuoret naiset, aggressiiviset histologiat, kookkaat rinnat) osalta
- Euroopassa on edelleen paikoin konservatiivisuutta liian rajoitetuksi tulkitusta näytön asteesta johtuen
- Suuntaus on sama kuin eturauhassyövässä – fraktion koko kasvaa edelleen samalla kun vaatimukset nykyaikaisimman ja normaalikudosystävällisen tekniikan käytöstä toteutuvat

Kiitos!