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13. Ulusal
Meme Hastalıkları
Kongresi *21-25 Ekim 2015*
Gloria Kongre Merkezi - Antalya

Meme Kanserinde Hipofraksiyonasyon

“Hipofraksiyone tüm meme RT”

Dr Merdan Fayda

1900-1920 Masif doz

*“ Radyasyon hasarı hücresel metabolizma ile olur.
Hızlı büyüyen tümör bağ dokusundan daha hızlı iyileşir.*

*Eğer kanserisidal doz bir fraksiyonda verilemezse
tümör büyür”*



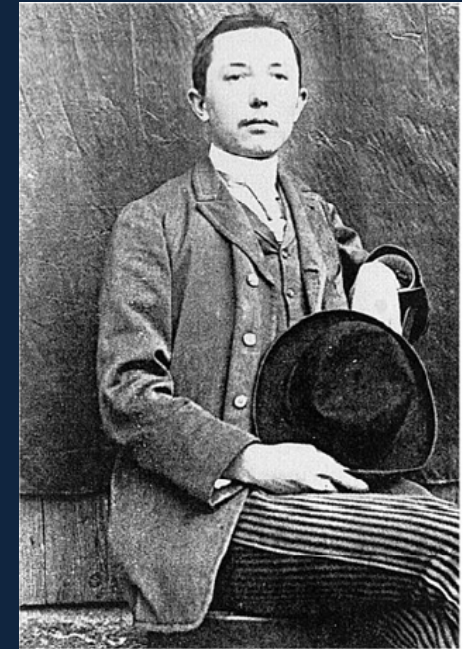
İlk Fraksiyonasyon :1920'ler

- Radyumun düşük doz hızı ile Masif dozlardan daha iyi sonuç elde etmesi X-ışını kullanıcılarını fraksiyonasyon deneylerine başlattı.
- Dr Regaud ve Coutard 1930'lar keçiye skrotumunu nekroze etmeden sterilize etmenin tek yolu fraksiyonasyon dediler



1930'lar

- Regaud'un Keçi deneyi sonrası Coutard Baş-boyun kanserinde küçük fraksiyonasyonlar ile
 - Daha iyi primer tümör kontrolü
 - Daha iyi 5yıl HSK
 - Daha az normal doku komplikasyonu



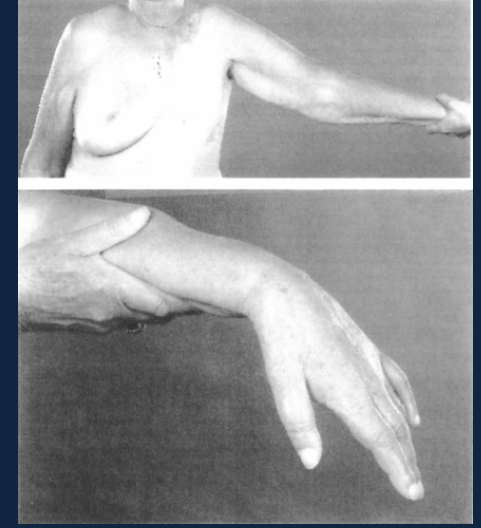
Dr. Regaud

Günümüzde pek çok standart RT tedavisi

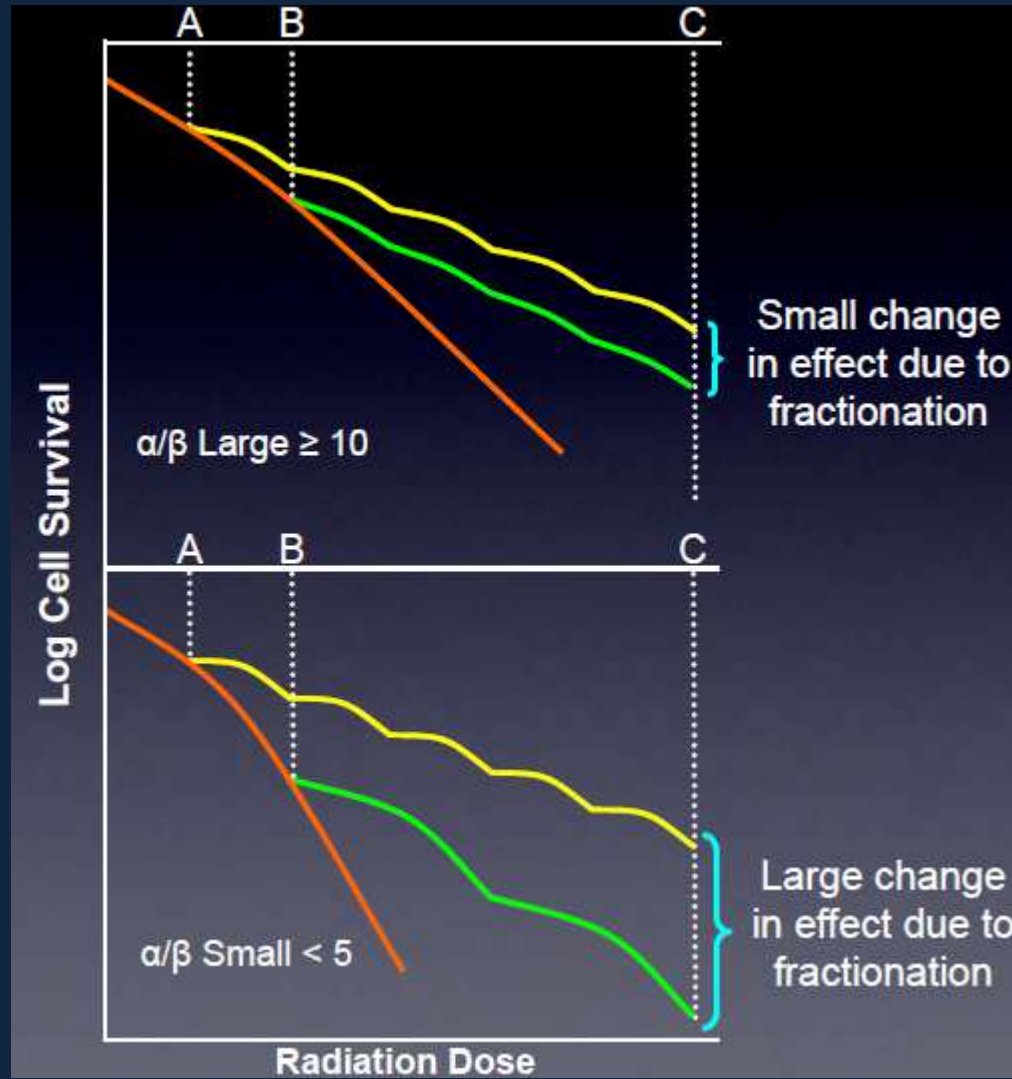
- Standart günlük fraksiyon dozları ile
 - 1.8-2 Gy / fr
- Konvansiyonel RT ile tipik adjuvan meme ca RT dozları
 - Meme ----- 45-50 Gy / 23-25 fr
 - Toraks cidarı----- 45-50 Gy / 23-25 fr
 - Tümör yatağı ek dozu-boost--- 10-16 Gy / 5-8 fr
 - Supra, level 1-3, MI ----- 46 Gy / 23 fr

Hipofx RT

- Brakiyal pleksopati 1970'ler



- Günlük fraksiyon yükseltilmiş ancak total doz düşürülmemiştir.



- Meme CA'da
 α/β oranı : 4,6
 (%95 GA 1,1 – 8,1)
 geç cevap veren dokulara yakın olduğundan hipofr.

Hipofraksiyonasyon Kanada çalışması

1234 hasta
Boost yok

612 hst 50 Gy / 25 fr (200cGy) / 35 gün

||||| ||||| ||||| ||||| |||||

622 hst 42,5 Gy / 16 fr (265cGy) / 22 gün

||||| ||||| ||||| |

1993-1996

Whelan, NEJM, 2010

Kanada çalışması

50 Gy/25fr – 42,5Gy/16fr

Hasta sayısı	1234 hst
Takip	12 yıl
	İnvazif tümör
	pT1-2 p N0 (aksiller küraj)
	CS – (mürekkep sınırda -)
MKC	% 100 (seperasyon < 25cm)
Kemoterapi	% 11 (CMF çoğunlukta)
Tamoksifen	% 42
Boost	YOK
Bölgesel RT	YOK

Kanada çalışması

50 Gy/25fr – 42,5Gy/16fr

	50 Gy / 25 fr	42,5 Gy / 16 fr
Lokal nüks 10 yıl	6,7	6,2
Sağkalım 10 yıl	84,4	84,6
Toksisite*, 5 yıl		
Cilt	% 17,7	%13,9
Subkutanöz doku	%38,6	%34,2
Toksisite*, 10 yıl		
Cilt	% 29,5	%33,2
Subkutanöz doku	%54,7	%51,9
Kötü kozmetik 10 yıl	28,7	30,2

*Grad 1-3 RTOG EORTC geç morbidite skorlaması

Whelan, NEJM, 2010

Kanada çalışması

50 Gy/25fr – 42,5Gy/16fr

Change in QOL at 4 weeks Post-RT

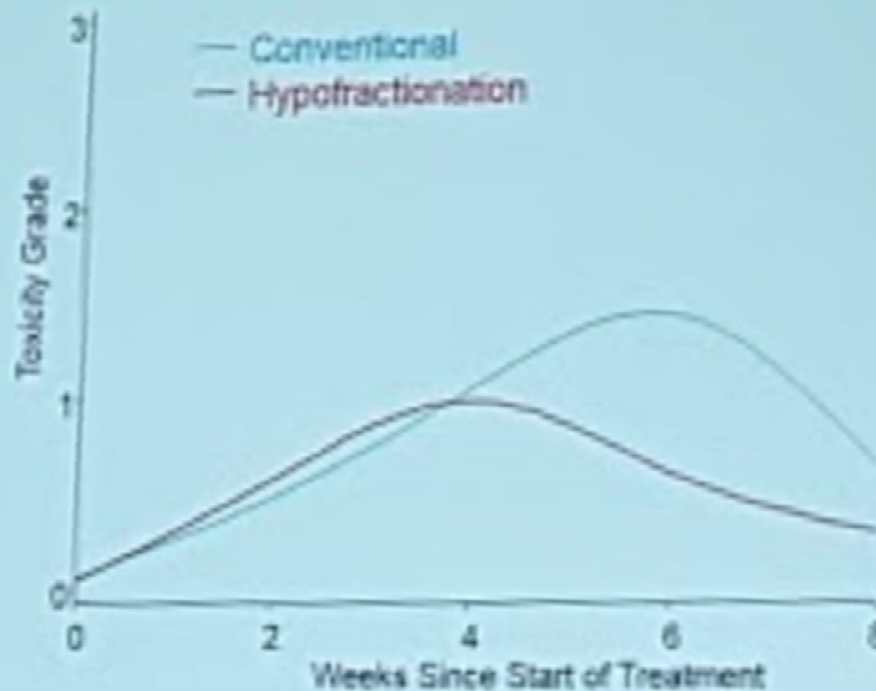
- ❖ 1152 of 1234 patients from main trial participated in QOL study
 - 563 randomized to Conventional WBI arm
 - 579 randomized to Hypofractionated WBI arm
- ❖ Hypofractionation resulted in improved overall QOL as well as QOL attributed to skin side effects, breast side effects, and attractiveness

QOL Domain	Treatment Effect for Change		P-value
	Mean	95% CI	
Overall QOL	.13	.04, .21	.003
Skin	.27	.12, .42	< .001
Breast	.22	.08, .36	.002
Attractiveness	.26	.13, .40	< .001

Kanada çalışması

50 Gy/25fr – 42,5Gy/16fr

ECOG Acute Skin Toxicity



- Statistically significant Treatment X Time interaction, $p < .001$
- Similar results were seen with the WHO grading system, $p < .001$

Hipofraksiyonasyon START-A

2236 hasta

749 hst 50 Gy / 25 fr (200cGy) / 5 hafta

||||| ||||| ||||| ||||| |||||

750 hst 41,6 Gy / 13 fr (320cGy) / 5 hafta

||| || ||| || |||

737 hst 39 Gy / 13 fr (300cGy) / 5 hafta

||| || ||| || |||

1999-2002

START A

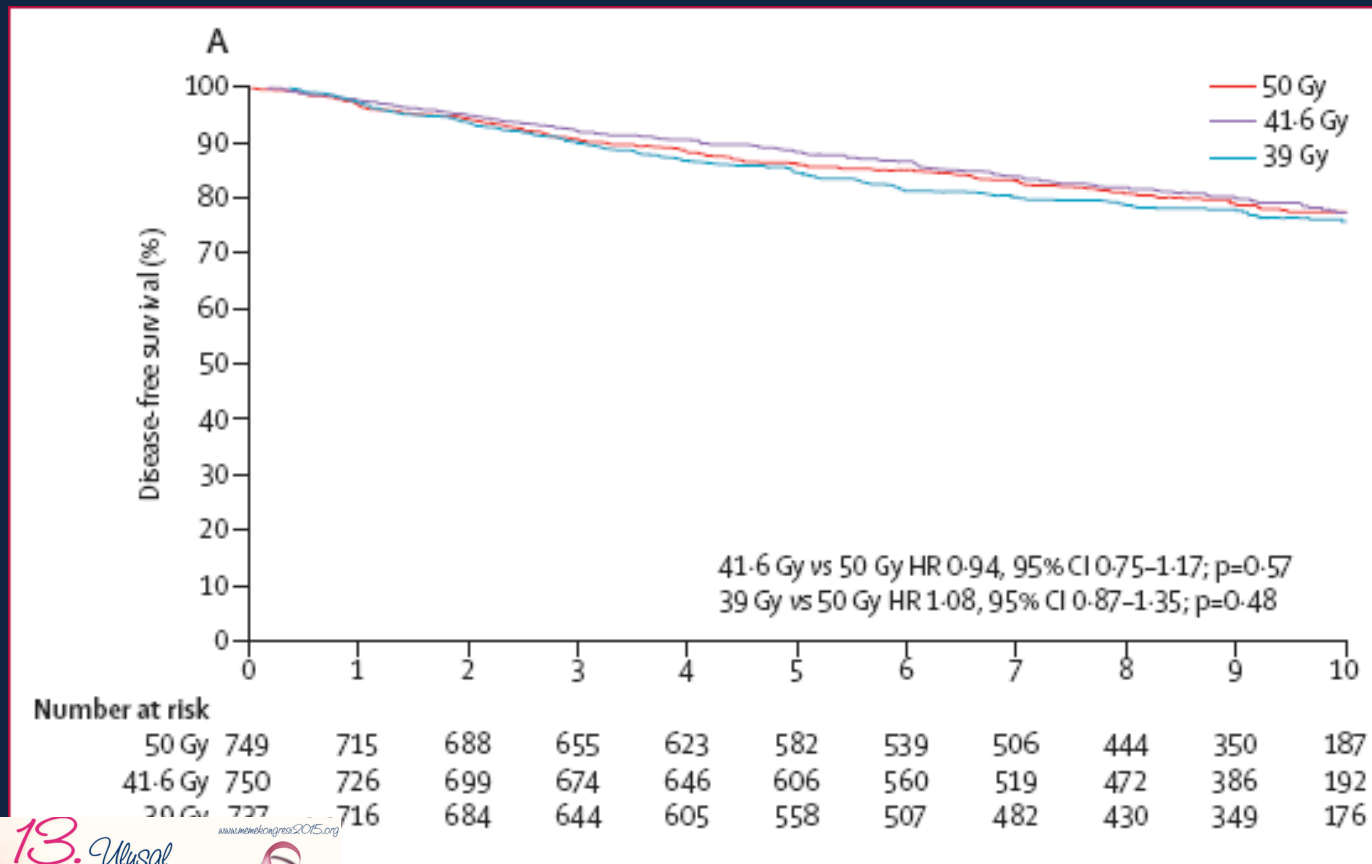
50 Gy/25fr – 41,6Gy/13fr/5hft – 39 Gy/13 fr/5hft

Hasta sayısı	2236 hst
Takip	9,3 yıl
	İnvazif tümör pT1-3 p N0-1
	CS – (≥ 1 mm) Aks disseksiyon %97
MKC	% 85
Mastektomi	%15
Nod pozitif	%29
Kemoterapi	% 36 (%70 antrasiklin temelli)
Tamoksifen	% 79
Boost	% 61
Bölgesel RT	% 14
ER, PR durumu	???

START A

50 Gy/25fr – 41,6Gy/13fr/5hft – 39 Gy/13 fr/5hft

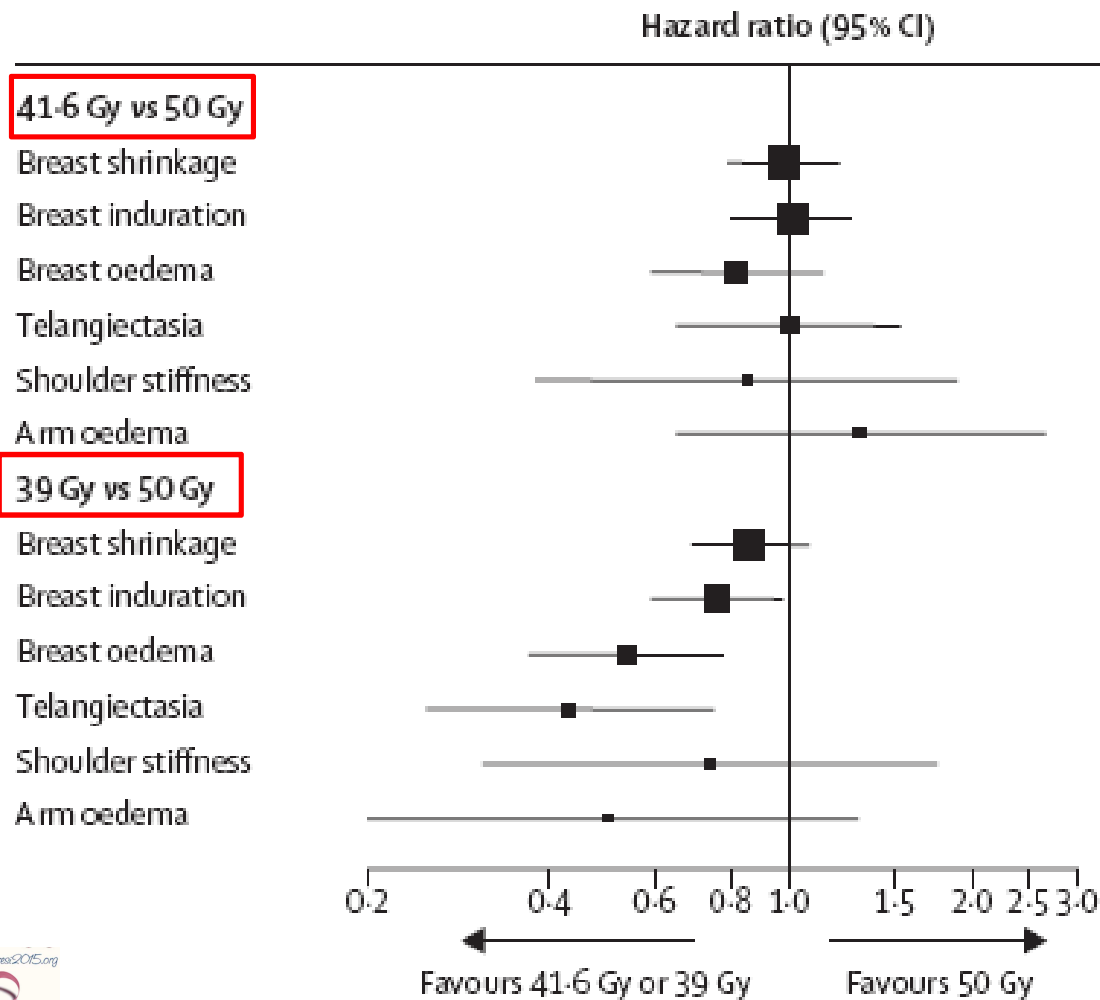
	50 Gy / 25 fr	41,6 Gy / 13 fr	39 Gy /13 fr
LBY 10y	% 7,4	% 6,3	%8,8



START A

50 Gy/25fr – 41,6Gy/13fr/5hft – 39 Gy/13 fr/5hft

A



Hipofraksiyonasyon START-B

2215 hasta

1105 hst 50 Gy / 25 fr (200cGy) / 5 hafta

||||| ||||| ||||| ||||| |||||

1110 hst 40 Gy / 15 fr (267cGy) / 3 hafta

||||| ||||| |||||

1999-2001

START B

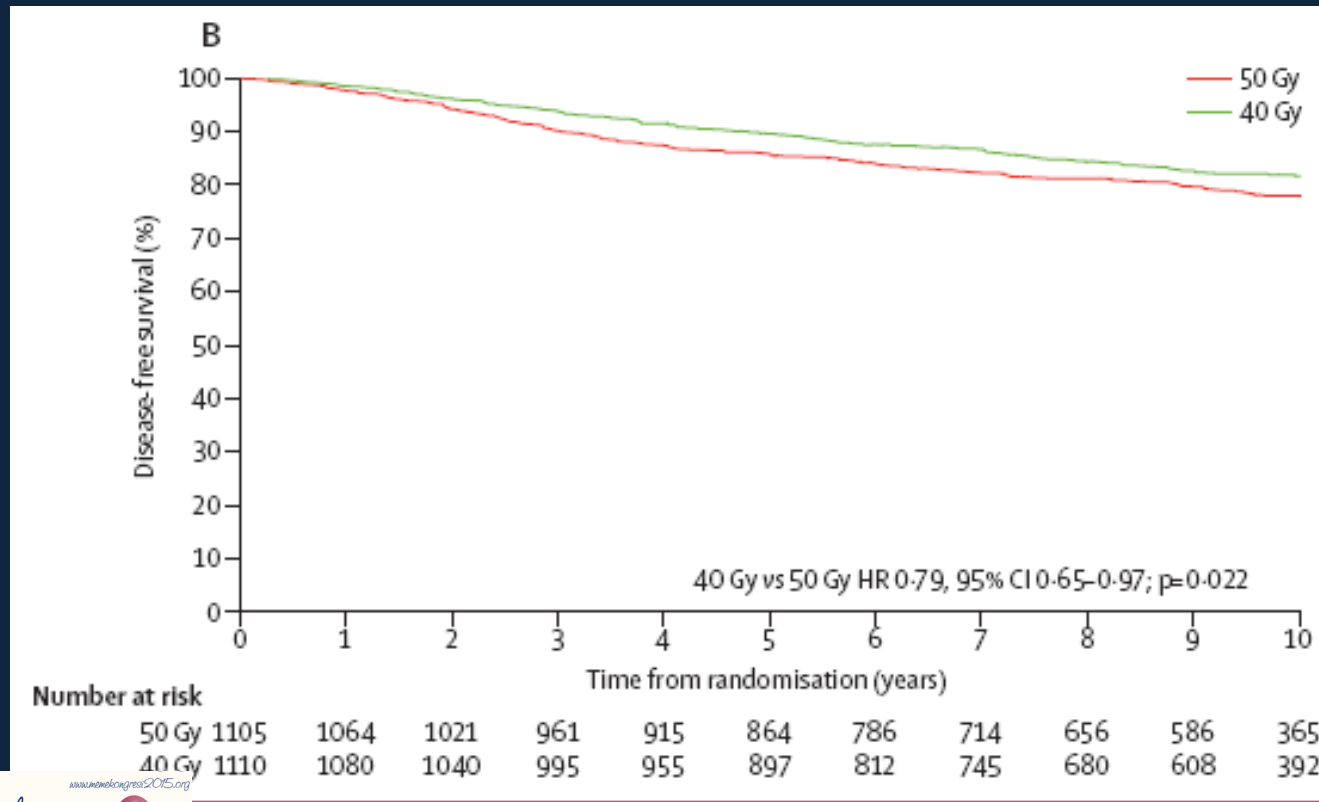
50 Gy/25fr – 40 Gy/15fr

Hasta sayısı	2215 hst
Takip	9,9 yıl
	İnvazif tümör pT1-3 p N0-1
	CS – (≥ 1 mm) Aks disseksiyon % 95,6
MKC	% 92
Mastektomi	% 7
Nod pozitif	% 23
Kemoterapi	% 22 (% 60 antrasiklin temelli)
Tamoksifen	% 87
Boost	% 42
Bölgesel RT	% 7
ER, PR durumu	???

START B

50 Gy/25fr – 40 Gy/15fr

	50 Gy / 25 fr	40 Gy / 15 fr
LBY 10y	% 5,5	%4,3



START B

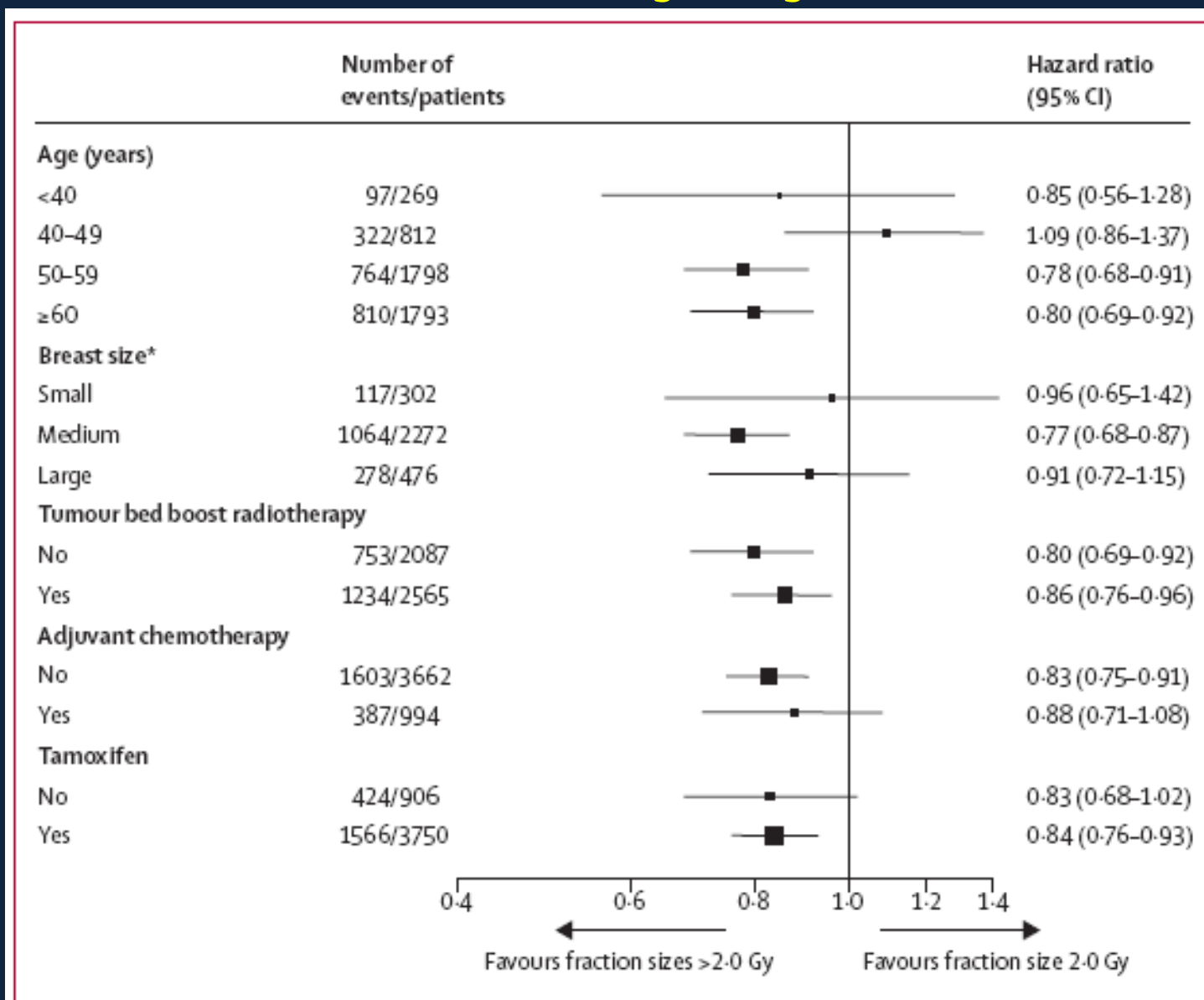
50 Gy/25fr – 40 Gy/15fr

	Events (n/patients; %)	Estimated proportion of patients with event by 5 years (%; 95% CI)	Estimated proportion of patients with event by 10 years (%; 95% CI)	Crude hazard ratio (95% CI)	p value*
Local relapse					
50 Gy	50/1105 (4.5%)	3.3% (2.4–4.6)	5.2% (3.9–6.9)	1.00	..
40 Gy	36/1110 (3.2%)	1.9% (1.2–3.0)	3.8% (2.7–5.2)	0.70 (0.46–1.07)	0.10
Local-regional relapse					
50 Gy	53/1105 (4.8%)	3.5% (2.5–4.8)	5.5% (4.2–7.2)	1.00	..
40 Gy	42/1110 (3.8%)	2.3% (1.5–3.4)	4.3% (3.2–5.9)	0.77 (0.51–1.16)	0.21
Distant relapse					
50 Gy	158/1105 (14.3%)	10.5% (8.8–12.5)	16.0% (13.8–18.5)	1.00	..
40 Gy	121/1110 (10.9%)	7.5% (6.0–9.2)	12.3% (10.3–14.6)	0.74 (0.59–0.94)	0.014
Any breast cancer-related event†					
50 Gy	222/1105 (20.1%)	14.3% (12.3–16.5)	22.2% (19.7–25.0)	1.00	..
40 Gy	182/1110 (16.4%)	10.4% (8.7–12.4)	18.3% (16.0–20.9)	0.79 (0.65–0.97)	0.022
All-cause mortality					
50 Gy	192/1105 (17.4%)	10.9% (9.1–12.9)	19.2% (16.8–21.9)	1.00	..
40 Gy	159/1110 (14.3%)	7.9% (6.4–9.6)	15.9% (13.7–18.4)	0.80 (0.65–0.99)	0.042

*Assessed with log-rank test compared with 50 Gy. †Local, regional, or distant relapse, breast cancer death, contralateral breast cancer.

ality according to fractionation schedule in START-B

START A-B çalışmaları



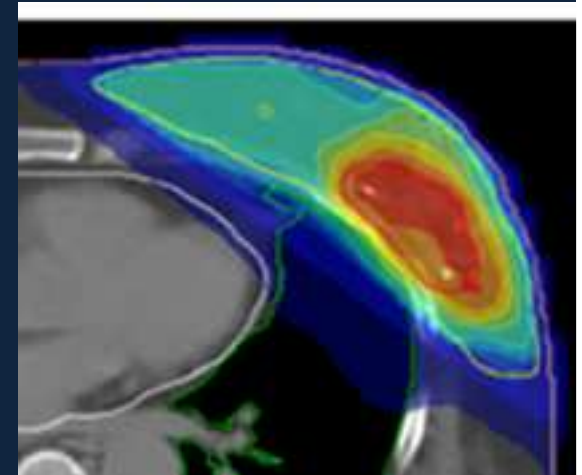
analysis of any moderate or marked physician-assessed normal tissue effects in the breast

Haviland, Lancet Oncol, 2013

Long-term Toxicity and Outcomes of Hypofractionated Radiation Therapy With an Incorporated Boost for Early-Stage Breast Cancer

[L. Wang](#), [C.T. Murphy](#), [E. Handorf](#), [G.M. Freedman](#), [M.E. Johnson](#), [T. Shaikh](#), [S.B. Hayes](#), [R.J. Bleicher](#), [L. Goldstein](#), [P.R. Anderson](#)
Fox Chase

- N=247 (75'i faz II) vs konv seri
- Tis-T2
- Evre 0-2
- IMRT tüm meme 45 Gy / 20 fr
boost 48 Gy / 20 fr
- Takip 52 ay



ASTRO, 2015

Aly, RO 2015

Long-term Toxicity and Outcomes of Hypofractionated Radiation Therapy With an Incorporated Boost for Early-Stage Breast Cancer

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Conclusion

The 4-week course of hypofractionated whole breast radiation with incorporated boost as compared to 6-week conventional fractionation with sequential boost:

- Associated with excellent long term local control
- Less observed acute toxicity
- Similar observed late toxicity
- Similar patient reported quality of life and cosmesis

IMRT tüm meme 45 Gy / 20 fr
boost 48 Gy / 20 fr
52 aylık takip

ASTRO, 2015

START A-B alıřmaları

- 40 Gy/15 fr hem meme hem de periferik lenfatik iin standart meme ca adjuvan tedavisidir.

Hypofractionated breast radiation: preferred standard of care?

Bruce G Hafty, Thomas A Buchholz

for all normal tissues.⁵ Thus, we agree with Haviland and colleagues that hypofractionation is a reasonable approach even when treating the regional lymph nodes. However, we also understand why many physicians might choose a more conservative approach as far more data are available about the standard regimen for treatment of regional lymph nodes. We also concur with

Hipofx RT

- ASTRO 2011 guideline

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 ($\pm 7\%$;) (as calculated with 2-dimensional treatment planning without heterogeneity corrections).

Hypofractionated Breast Irradiation

Following breast conserving surgery, hypofractionated whole breast irradiation may be used in:

- Patients aged 50 years or older without prior chemotherapy or axillary lymph node involvement

89/2/9 %

1Y/ 2N/ 9A

- Patients younger than 50 years

71/2/27%

1Y/ 2N/ 9A

- Those with prior chemotherapy or axillary lymph node involvement

51/18/31 %

1Y/

2N/ 9A

Hipofx RT - Teknik

- Meme boyutu
 - Kanada çalışması (Seperasyon < 25cm)
 - START A ve B çalışmalarında her üç boyuttan meme mevcut.

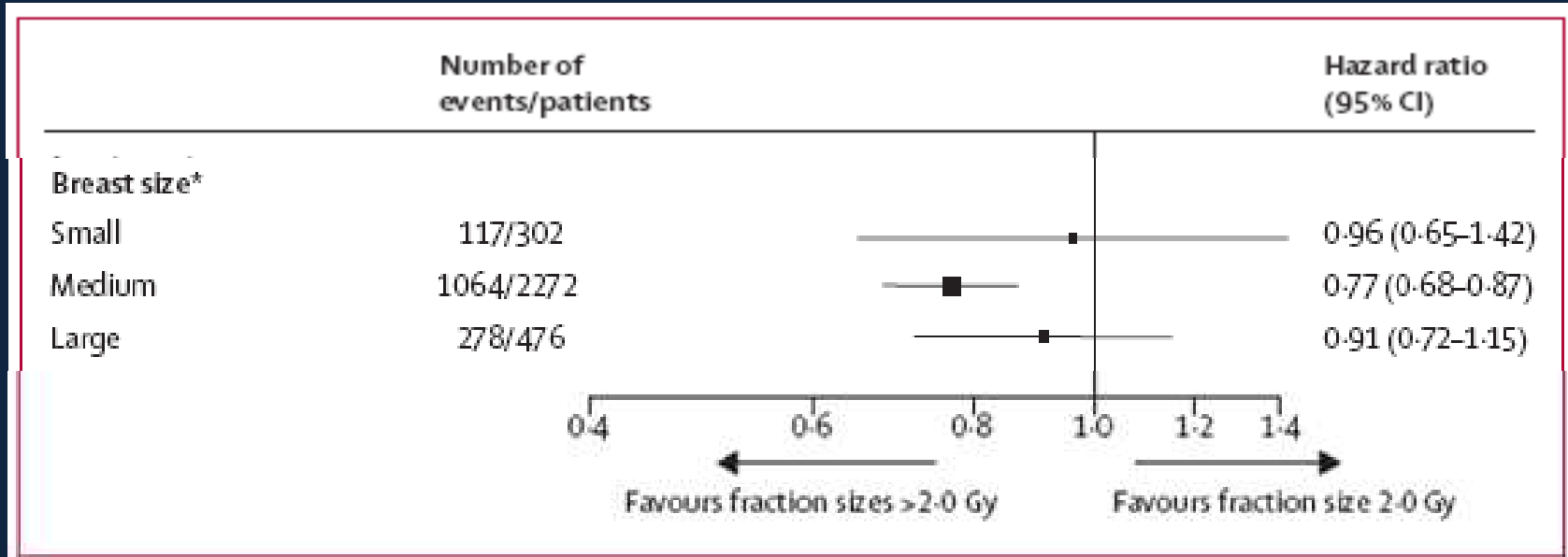


Figure 5: Meta-analysis of any moderate or marked physician-assessed normal tissue effects in the breast

Hipofx RT - Teknik

- Tümör yatağı boostu
 - Kanada çalışmasında yok
 - START A (%61) ve B'de (%42) var.
 - Uygun elektron enerjisi ile %100 izodoz hattına tanımlanmış. 10 Gy / 5fr
 - 2,5Gy x 2-4 fr verilebilir

Hipofx RT - Teknik

- Toraks duvarı
 - Kanada çalışmasında yok
 - START A (%15) ve B'de (%8) var.
 - PM anında rekonstruksiyonlu hastalar alınmamış
 - Uygulanabilir

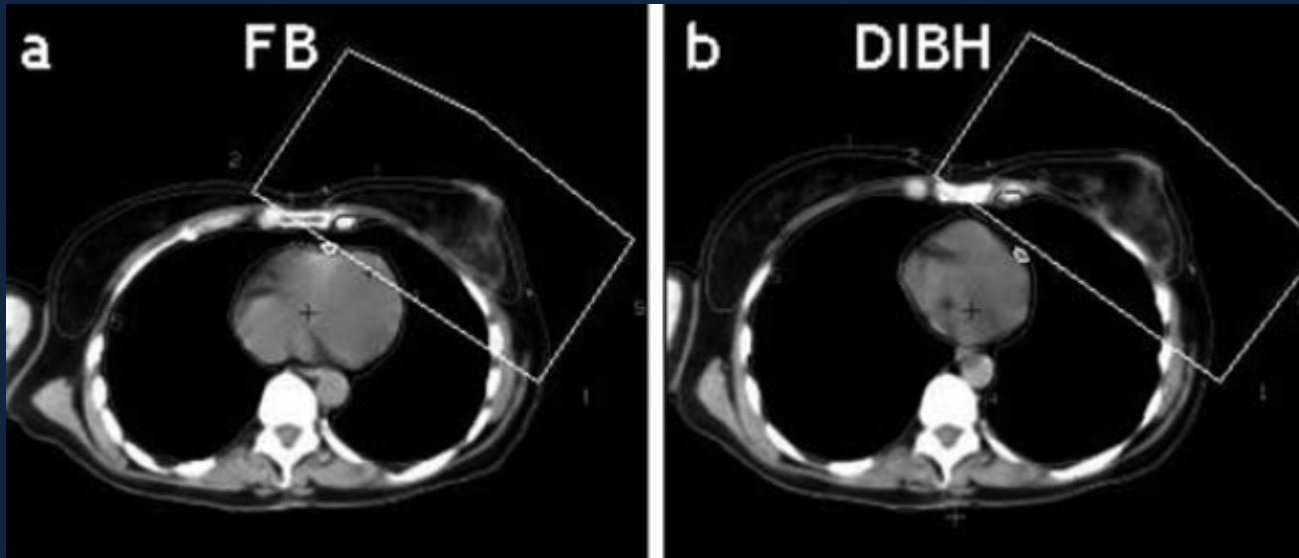
Hipofx RT - Teknik

- Gecikmiş kardiyotoksisite
 - > 15 yıl takip gerekir.

	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)
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%)

Hipofx RT - Teknik

- Gecikmiş kardiyotoksisite
 - > 15 yıl takip gerekir.
 - Ancak modern RT'de direkt alan içerisinde zaten hiç kalp yok.



Hipofx RT - Teknik

- Brakiyal pleksopati
- Lenfatik RT Kanada çalışmasında yok
- START A (%14)ve B'de (%7,3)

	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)
Brachial plexopathy	0	1 (0.1%)	0	1 (<0.1%)	0	0	0

Hipofx RT - Teknik

- Semptomatik kaburga kırığı, akciğer fibrozisi
- Farksız

	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)

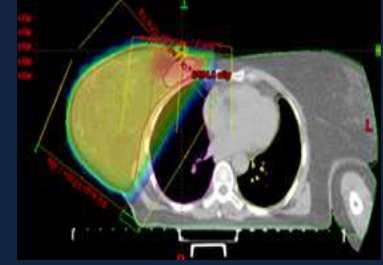
Symptomatic rib fracture*

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%)

Hipofix RT - Teknik



- Doz homojenitesi
 - + / - %7 günümüz teknolojisi ile sağlanması kolay.
 - Kanada çalışması 2 B planlama
 - START A-B 2B ya da 3B planlama

Özet

- Memeye tüm yaşlarda hipofx RT (40-42,5Gy / 15-16fr) düşünülebilir (NCCN 2015 hipofx önce öneriyor) (< 50 y?).
- Toraks duvarı (nonrekonstrakte) hipofx RT düşünülebilir (NCCN 2015 hipofx önce önermiyor) .
- Supra+/- aksilla düşünülebilir (NCCN 2015 lenfatik Hipofx önermiyor).
- Boost (42,5Gy/16 fr sonrası 2,5Gy x2-4fr)
- (faz-2 tüm meme 45 Gy / 20 fr
eş zamanlı boost 48 Gy / 20 fr)
RTOG 1005 (yayınlanmadı meme 40Gy/15fr, 48Gy/15fr eş z boost)
- Kemoterapi hipo fx RT için engel değil