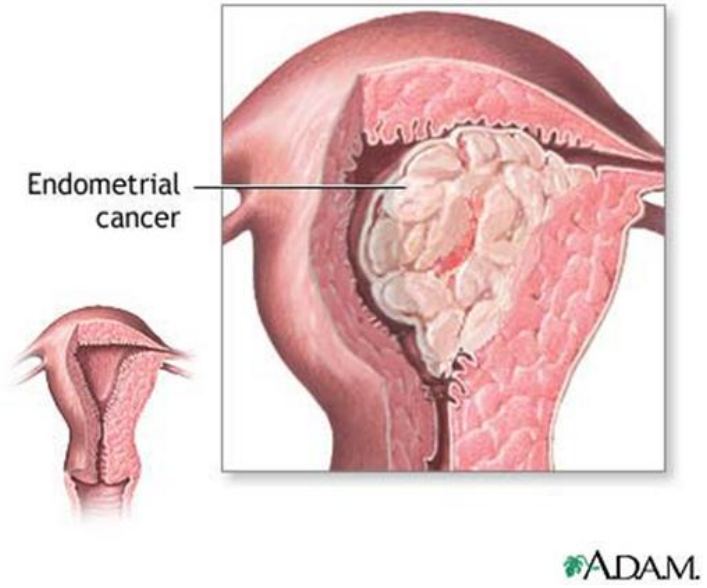
Endometrium Kanseri Tedavisindeki Gelişmeler - RADYOTERAPİ



Dr.Zeynep Özsaran

E.Ü.T.F. Radyasyon Onkolojisi AD

Sunum Akışı

- Endometrium kanserinin tedavisine genel bakış
- Adjuvan tedavi kararındaki risk faktörleri
- Erken evre endometrium kanserinde radyoterapi
- İleri evre endometrium kanserinde radyoterapi
- Sonuç

Endometrium kanseri

- Endometrium kanserinin
  -evrelemesi,
  -cerrahi yaklaşımları
  -adjuvan tedavisinde

son yıllarda değişim yaşanmaktadır

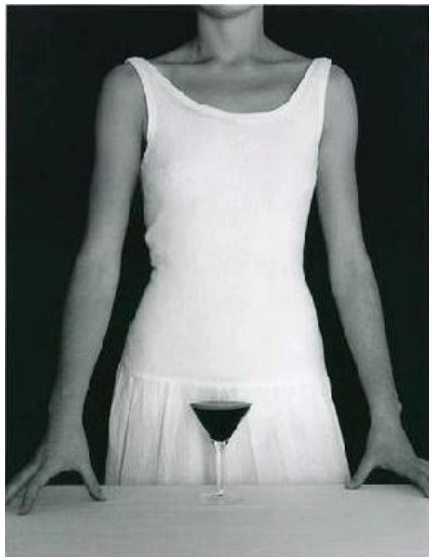
- Cerrahi halen esas tedavidir
- Radyoterapi lokal kontrolde önemini korumakta
- Kemoterapi ise yüksek riskli ve ileri evre olgularda giderek daha fazla ön plana çıkmaktadır

Endometrium Kanserinde Güncel Yaklaşım

- Uygun Preopertatif Değerlendirme
- Etkin Cerrahi Tedavi ve Evreleme
  - Geniş İnsizyon / İyi Explorasyon
  - Peritoneal Sitoloji Alınması
  - En az Tip I Histerektomi + BSO
  - İntraoperatif değerlendirme;
    - tümör büyüklüğü, myometrial invazyon derinliği, servikal tutulum
  - Pelvik ve Paraaortik Lenfadenektomi
  - Omentektomi & Şüpheli alanlardan Biopsiler
- Prognostik Faktörlerin Belirlenmesi
- Uygun Adjuan Tedavinin Planlanması
  - Radyoterapi; External; Pelvik/Paraaotik, İnternal
  - Kemoterapi

Radikal Cerrahi herzaman mümkün değil!!

- 60-85 yaş kadınlarda sık görülmekte
- Hastaların büyük çoğunluğu
  - diabet
  - obesite
  - kardiovasküler hastalık gibi



Komorbiditelere sahip

Cerrahi ile İlgili Sorular?

- Lenfadenektomi?

- Basit Histerektomi Sonrası Yeniden Evreleme?

Basit Histerektomi Sonrası Endometrium Kanseri Tanısı Alanlarda Yaklaşım Seçenekleri;

1- Yeniden Evreleme Cerrahisi ile Prognostik Faktörlerin Belirlenmesi

TÜM OLGULARA LENFADENEKTOMİ

YAPILMALIDIR	YAPILMAMALIDIR
Kilgore, 1995	Eltabbakh , 1997
Frumovitz, 2004	Mohan, 1998
Cragun, 2005	Mariani, 2000
Ben-Shachar, 2005	Cragun, 2005
Lutman, 2006	Watari, 2005
Chan, 2006	Panicci 2008
	Kitchener, 2009
	May, 2010 (Cochrane)

Available online at www.sciencedirect.com
ScienceDirect
Gynecologic Oncology 106 (2007) 282–288
Gynecologic Oncology
www.elsevier.com/locate/ygyno

The outcomes of 27,063 women with unstaged endometrioid uterine cancer

John K. Chan [a,*], Huahsi Wu [b], Michael K. Cheung [b], Jacob Y. Shin [b], Kathryn Osann [d], Daniel S. Kapp [c]

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Received 21 March 2007

12333 LND (+) vs. 27063 LND (-)

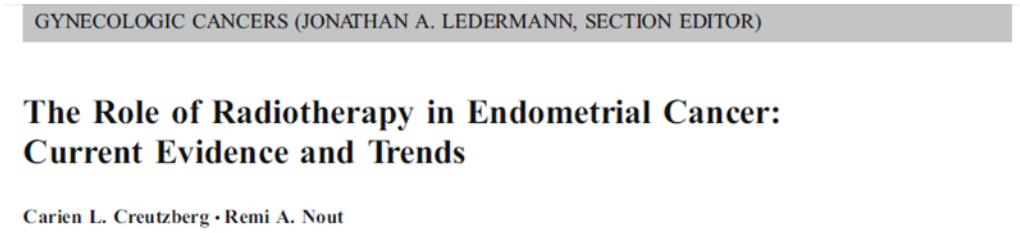
- **Sağkalım Süresi;**
  - ✓ **Evre > I ya da grade 3 hastalıkta fark var (p<0.001)**
  - ✓ **Evre I ve grade 1 - 2 hastalıkta fark yok (p = 0.26)**

Lenfadenektomi??

- Erken evrede örnekleme yeterli
- Ancak operasyon öncesi erken evre olduğunu anlamak herzaman mümkün değil
- 2 randomize çalışmada erken evrede sağkalım katkısı gösterilmemiş

ASTEC 2008

Benedetti et al.2009


GYNECOLOGIC CANCERS (JONATHAN A. LEDERMANN, SECTION EDITOR)

The Role of Radiotherapy in Endometrial Cancer: Current Evidence and Trends

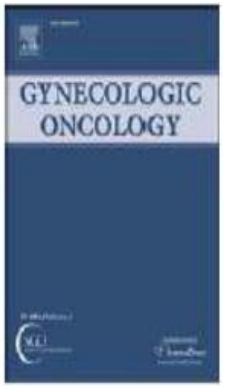
Carien L. Creutzberg · Remi A. Nout

Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer

S.C. Dowdy [a,*], B.J. Borah [b], J.N. Bakkum-Gamez [a], A.L. Weaver [c], M.E. McGree [c], L.R. Haas [b], G.L. Keeney [d], A. Mariani [a], K.C. Podratz [a]

[a] Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN 55905, USA

Gynecologic Oncology 127 (2012) 5–10



Mayo Düşük Risk Kriterleri; Tip I histoloji, Grade I-II, MI ≤ %50, Tümör ≤ 2cm

Table 2
Intra- and postoperative variables assessed as a function of whether surgical management included lymphadenectomy.

Parameters	Lymphadenectomy		Total (N = 385)	P-value[a]
	No (N = 305)	Yes (N = 80)		
Surgical approach, N (%)				<0.001
No laparotomy	24 (7.9)	5 (6.3)	29 (7.5)	
Laparotomy	210 (68.9)	75 (93.8)	285 (74.0)	
Vaginal only	71 (23.3)	-	71 (18.4)	
OR time (minutes)				<0.001
Mean (SD)	108.0 (52.9)	150.6 (71.8)	116.8 (59.8)	
Median (IQR)	96.0 (71.0, 130.0)	137.0 (112.5, 170.5)	104.0 (75.0, 143.0)	
Estimated blood loss (ml)				<0.001
Mean (SD)	231.6 (193.7)	309.9 (190.7)	247.9 (195.4)	
Median (IQR)	200.0 (100.0, 300.0)	250.0 (200.0, 400.0)	200.0 (100.0, 300.0)	
Length of hospital stay (days)				<0.001
Mean (SD)	3.3 (2.6)	3.7 (1.7)	3.4 (2.4)	
Median (IQR)	3.0 (2.0, 4.0)	3.0 (3.0, 4.0)	3.0 (2.0, 4.0)	
30-Day postoperative complications[c], N (%)				0.002[b]
None	246 (80.7)	50 (62.5)	296 (76.9)	
Grade 1	28 (9.2)	17 (21.3)	45 (11.7)	
Grade ≥ 2	31 (10.2)	13 (16.3)	44 (11.4)	

Table 3
Overall, recurrence-free and cause-specific survival as a function of whether surgical management included lymphadenectomy in low-risk endometrial cancer.

Outcome	Lymphadenectomy		*P*-value[a]
	No ($N=305$)	Yes ($N=80$)	
Overall survival			0.72
No. of events	25	6	
Estimate at 5 years	92.1%	94.2%	
Recurrence-free survival			0.64
No. of events	8	3	
Estimate at 5 years	97.6%	96.0%	
Cause-specific survival			0.32
No. of events	3	2	
Estimate at 5 years	99.0%	97.3%	

Table 4
Thirty-day median cost equated to 2010 Medicare dollars as a function of surgical management.

Parameters	Lymphadenectomy		*P*-value[a]
	No ($N=305$)	Yes ($N=80$)	
Surgical approach, Median (IQR)			
Laparotomy	$11,341.29 (10186.35–12906.88)	$15,439.62 (12941.82–18082.49)	<0.001
Minimally invasive	$11,663.37 (10750.55–13112.68)	$17,163.25 (16694.68–20593.74)	0.012
Vaginal only	$9043.57 (8493.28 -10645.39)	–	
Overall 30-day cost, Median (IQR)	$11,028.29 (9777.96–12731.73)	$15,678.09 (13104.76–18098.79)	<0.001

Lymphadenectomy for the management of endometrial cancer (Review)

Cochrane Database of Systematic Reviews 2010, Issue 1. Art. No.: CD007585.

May K, Bryant A, Dickinson HO, Kehoe S, Morrison J

THE COCHRANE COLLABORATION®

Analysis 1.1. Comparison 1 Survival, Outcome 1 Overall survival.

Review: Lymphadenectomy for the management of endometrial cancer

Comparison: 1 Survival

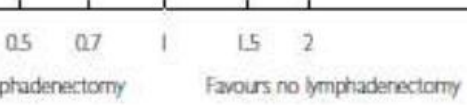
Outcome: 1 Overall survival

Study or subgroup	Lymphadenectomy N	No lymphadenectomy N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
Kitchener 2009	670	667	0.04 (0.17)		73.1 %	1.04 [0.75, 1.45]
Panici 2008	264	250	0.15 (0.28)		26.9 %	1.16 [0.67, 2.01]
Total (95% CI)					**100.0 %**	**1.07 [0.81, 1.43]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



Lenfadenektomi

- Lokal ileri evrede over kanserine benzer şekilde tedavinin önemli bir komponenti

- Sağkalım avantajı sağlamakta

Sitoredüksiyon ileri evrede prognostik faktördür

Aalders JG. Gynecol Oncol 1988
Chi DS. Gynecol Oncol 1997
van Wijk FH. Int J Gynecol Cancer 2006

Cerrahi Sonrası Tedavi Kararını Belirleyen Prognostik Faktörler

- Genellikle olgular erken evrede tanı almakta
- Adjuvan tedavi postoperatif prognostik faktörlere göre belirlenmektedir

Prognostik faktörler

- Evre hariç tutulduğunda en önemli prognostik faktör bölgesel lenf bezi yayılımıdır

- Kanserden ölüm ve yineleme riskini belirleyen diğer prognostik faktörler:

  - myometrial invazyon

  - tümör derecesi

  - lenfovasküler invazyon

  - histolojik tip (seröz papiller, clear cell)

  - ileri yaş

Endometrium kanseri
Pelvik LN metastaz riski

Evre	Gr1	Gr2	Gr3
IA	0.4%	0.46%	2.97%
IB	1.2%	3%	5.4%
IC	15%	15.7%	23.8%

FIGO, 1998

Endometrium kanseri
PA LN metastaz riski

	Gr1	Gr2	Gr3
IA	0%	0.5%	1.9%
IB	0.17%	0.76%	2.42%
IC	3.5%	6%	10.2%

FIGO,1998

Diğer Prognostik faktörler

- ***Histolojik tip***

  5 yıllık sağkalım;

  - endometrioid tip %92
  - nonendometrioid tip %33

- ***Lenfovasküler invazyon***

  5 yıllık sağkalım

  - LVI (+) % 64
  - LVI (-) %83

- ***Servikal tutulum***

  varlığında yineleme riski RR 1.6

Risk Tanımlamaları

- ***Düşük risk:*** endometriumda sınırlı veya ½ iç invazyon, derece1-2

- ***Düşük-orta risk:*** geri kalan olgular

- ***Orta –Yüksek risk:*** -70 yaşın üzerinde: en az 1 kötü risk faktörü
  - 50 yaş üzerinde en az 2 kötü risk faktörü
  - herhangi bir yaş 3 kötü risk faktörü

(Kötü risk faktörleri: derece 3, invazyon >1/2,lenfovasküler invazyon)

Yüksek risk: IIB-IVB veya Seröz papiller,Clear cell

Radyoterapi

ADJUVAN TEDAVI

Erken evre endometrium kanseri adjuvan tedavi

Randomize çalışmalar

	Sample size	Inclusion criteria	Surgery	Treatment	Locoregional recurrence	Overall survival
Norwegian Radium Hospital[57]	540	Stage I (all)	TAH or BSO	Brachytherapy *vs* brachytherapy and pelvic radiotherapy	7% *vs* 2% (5 year) p<0·01	89% *vs* 91% (5 year) p=NS
PORTEC-1[55]	715	Stage IB (grade 2, 3), stage IC (grade 1, 2)	TAH or BSO (LNS allowed)	Observation *vs* pelvic radiation	14% *vs* 4% (5 year), p<0·0001	85% *vs* 81% (5 year), p=0·31
GOG 99[56]	392	Stage IB, stage IC, stage II occult	TAH or BSO or LNS	Observation *vs* pelvic radiation	12% *vs* 3% (2 year), p=0·007	86% *vs* 92% (4 year), p=0·55
ASTEC[58]	905	Stage IA or IB (grade 3), IC, IIA	TAH or BSO with or without LNS	Observation *vs* pelvic radiation	6·1% *vs* 3·2% (5 year), p=0·02	84% *vs* 84% (5 year), p=0·31
PORTEC-2[59]	427	Stage IC (grade 2, 3, age >60 years), IB (grade 3, age >60 years), IIA	TAH or BSO with or without LNS	Brachytherapy *vs* pelvic radiation	5·1% *vs* 2·1% (5 year), p=0·42	86% *vs* 82% (5 year), p=0·66

TAH=total abdominal hysterectomy. BSO=bilateral salpingo-oophorectomy. LNS=lymph node surgery. NS=not significant.

***Table 3*: Randomised controlled trials of adjuvant therapy for intermediate-risk endometrial cancer**

1 metaanaliz mevcut

REVIEW

Adjuvant Radiotherapy for Stage I Endometrial Cancer: An Updated Cochrane Systematic Review and Meta-analysis

Anthony Kong,* Nick Johnson, Henry C. Kitchener, Theresa A. Lawrie*

Manuscript received April 19, 2012; revised July 23, 2012; accepted July 25, 2012.

*Authors contributed equally to this work.

Correspondence to: Anthony Kong, MBBS, MRCP, FRCR, PhD, Department of Oncology, University of Oxford, and Oxford University Hospitals NHS Trust, Oxford, UK (e-mail: anthony.kong@oncology.ox.ac.uk) and Theresa A. Lawrie, MBChB, PhD, The Cochrane Gynaecological Cancer Review Group, Royal United Hospital, Bath, UK (e-mail: tlawrie@nhs.net).

Background The role of adjuvant radiotherapy in stage I endometrial cancer has changed in recent years. This updated Cochrane systematic review aimed to reexamine the efficacy and toxicity of adjuvant radiotherapy vs no treatment in stage I endometrial cancer.

Methods We searched various databases including The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and the Specialised Register of the Cochrane Gynaecological Cancer Review Group (CGCRG) for randomized controlled trials that met the predefined inclusion criteria. The primary outcome was overall survival (OS); secondary outcomes were endometrial cancer–specific survival, locoregional recurrence, distant recurrence, and toxicity. Hazard ratios (HRs) were estimated and pooled if possible; otherwise, dichotomous data were extracted. All statistical tests were two-sided.

Results Of the eight included trials, seven trials (3628 women) compared external beam radiotherapy (EBRT) and no EBRT (or vaginal brachytherapy [VBT]), and one trial (645 women) compared VBT and no additional treatment. EBRT statistically significantly reduced locoregional recurrence compared with no EBRT (or VBT alone) (HR = 0.36, 95% confidence Interval [CI] = 0.25 to 0.52; $P < .001$), but this did not translate into an improvement in OS (HR = 0.99, 95% CI = 0.82 to 1.20; $P = .95$), endometrial cancer–specific survival (HR = 0.96, 95% CI = 0.72 to 1.28; $P = .80$), or distant recurrence rates (risk ratio = 1.04, 95% CI = 0.80 to 1.35; $P = .77$). EBRT was associated with an increased risk of severe acute toxicity, severe late toxicity, and reduced quality of life scores.

Conclusions EBRT reduces the risk of locoregional recurrence but has no statistically significant impact on cancer-related deaths or OS. However, EBRT is associated with clinically and statistically significant morbidity and a reduction in quality of life.

J Natl Cancer Inst 2012;104:1625–1634

Sağkalım

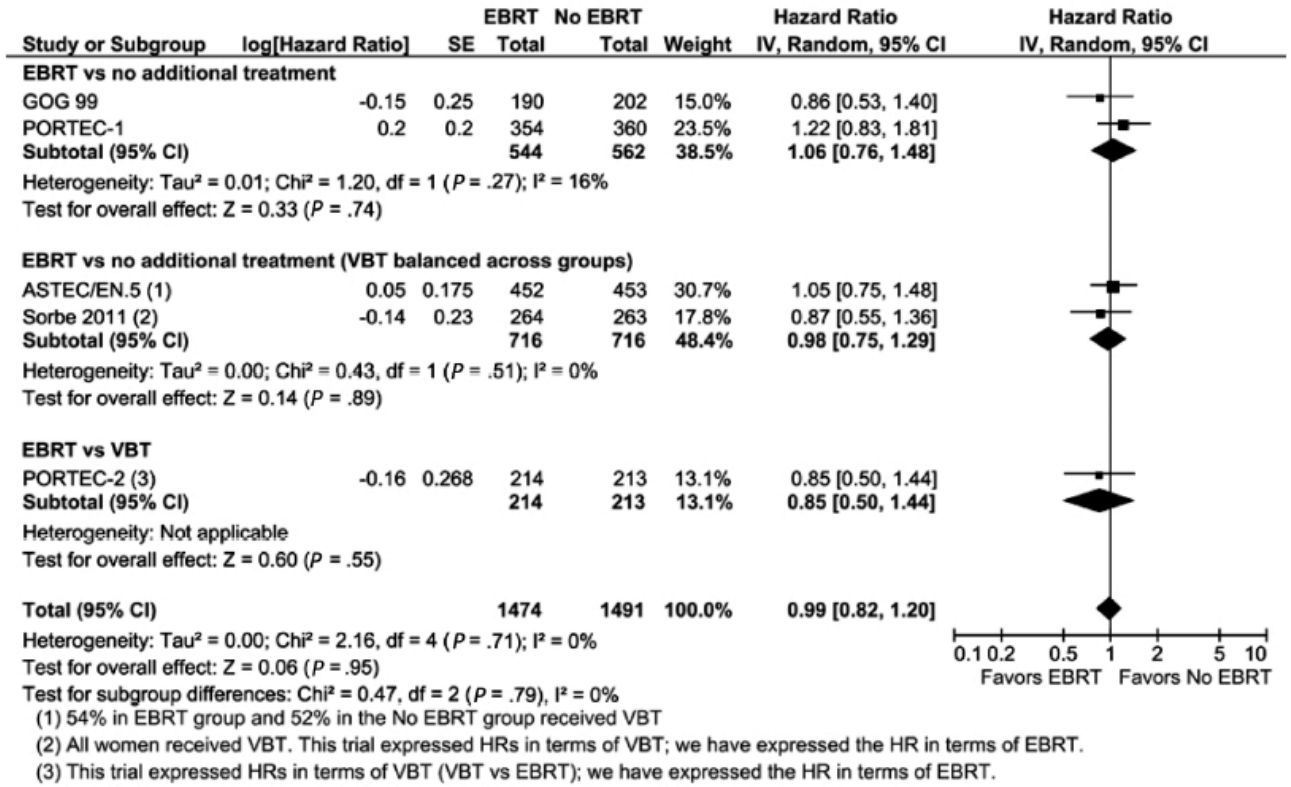


Figure 2. Forest plot of hazard ratios (HRs) comparing overall survival (OS) for stage I endometrial carcinoma patients who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the **squares**, the size of the square represents the weight of the trial in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, *P* values, and the test for overall effect; these calculations were two-sided. The χ^2 test was used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.

Lokal-bölgesel kontrol

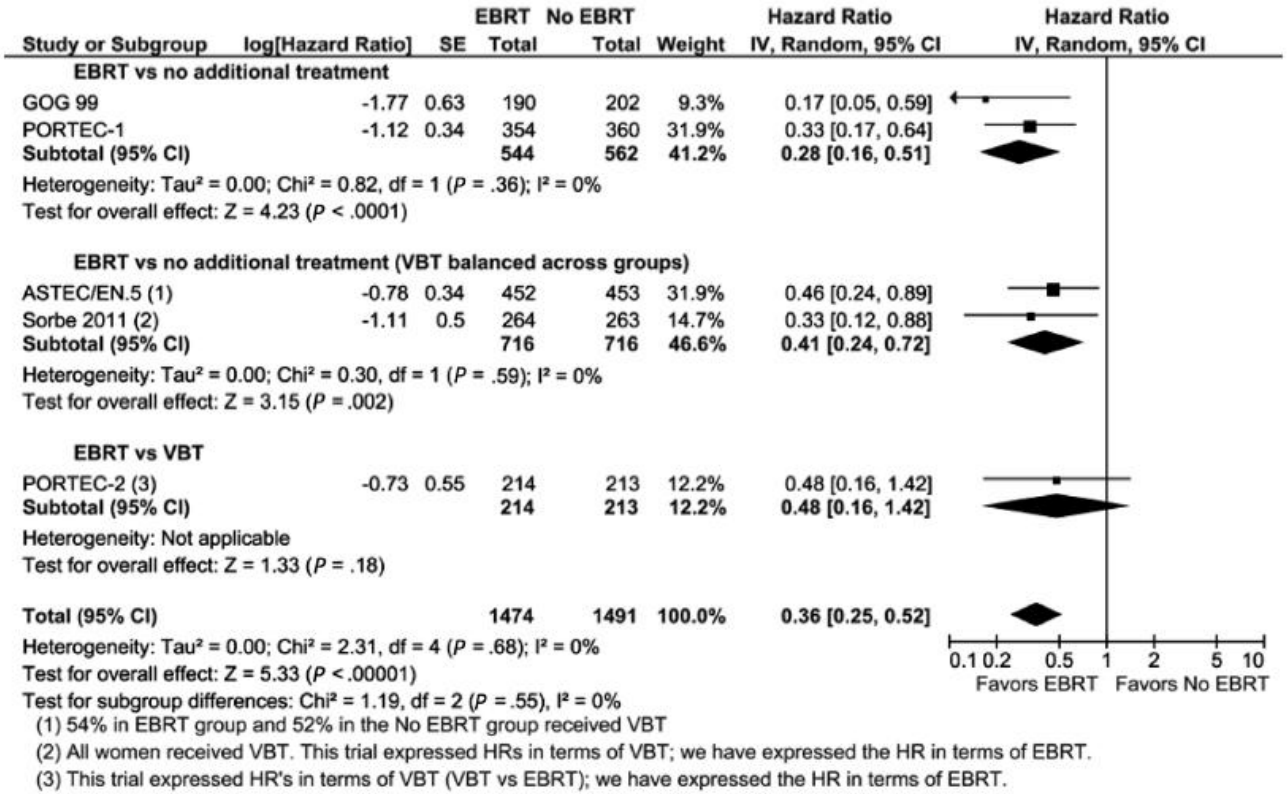


Figure 3. Forest plot of hazard ratios (HRs) comparing the locoregional recurrence for stage I endometrial carcinoma patients who received external beam radiotherapy (EBRT) treatment vs those who received no EBRT treatment. HRs for each trial are represented by the **squares**, the size of the square represents the weight of the trial in the meta-analysis, and the **horizontal line** crossing the square represents the 95% confidence interval (CI). The **diamonds** represent the estimated overall effect based on the meta-analysis random effect of all trials. Inverse variance (IV) and random effects methods were used to calculate HRs, 95% CIs, *P* values, and the test for overall effect; these calculations were two-sided. The χ^2 test and the I^2 statistic were used to calculate heterogeneity. Random = random effects method; SE = standard error; VBT = vaginal brachytherapy.

PORTEC -1

International Journal of Radiation Oncology*Biology*Physics
Volume 81, Issue 4, 15 November 2011, Pages e631–e638

Clinical Investigation

Fifteen-Year Radiotherapy Outcomes of the Randomized PORTEC-1 Trial for Endometrial Carcinoma

Presented in part at the 51th Annual Meeting of the American Society for Therapeutic Radiology and Oncology, Chicago, IL, November 2009. and at the 16th International Meeting of the European Society for Gynaecological Oncology, Belgrade, Serbia, October 2009.

- *15 yıllık lokal yineleme oranları*
  - RT kolunda %6
  - gözlem kolunda %15.5 p<0.001

- *15 yıllık sağkalım*
  - RT kolunda %60
  - gözlem kolunda %52 p=0.31

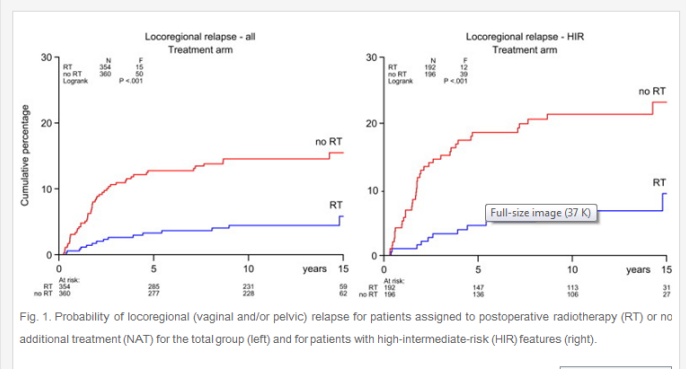


Fig. 1. Probability of locoregional (vaginal and/or pelvic) relapse for patients assigned to postoperative radiotherapy (RT) or no additional treatment (NAT) for the total group (left) and for patients with high-intermediate-risk (HIR) features (right).

- *Komplikasyon*
  - RT kolunda %25
  - gözlem kolunda %6 p<0.0001

En önemli prognostik faktörler: grade3, >60 yaş, >1/2 invazyon

GOG 99 Çalışması

- 190 olgu
- Evre IB-IIB grade 1-3
- TAH+BSO+pelvik yıkama,pelvik-paraaortik lenf bezi örneklemesi yapılmış

- Randomizasyon
  - → 50.4 Gy RT (1.8 Gy fraksiyon dozu)
  - → Gözlem

GOG 99

- 2 yıllık lokal yineleme oranları
  - RT kolunda %3
  - gözlem kolunda %12 p<0.007

- 4 yıllık sağkalım
  - RT kolunda %92
  - gözlem kolunda %86 p=0.557

- Komplikasyon oranları RT grubunda yüksek

- *Yüksek riskli olgularda lokal yineleme* *%26*
  %6

ASTEC/CTG EN 5

Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis

- Evre IC, IIA veya IA-IIA / HG III olgular veya seröz papiller/clear cell – 906 olgu
- TAH+BSO lenf bezi kararı merkezlere göre değişiyor

- Randomizasyon
  - → 40-46 Gy RT (1.8 Gy fraksiyon dozu)
  - → Gözlem (%51 olguda brakiterapi)
- Sağkalım farkı yok
- Toksisite RT kolunda fazla

ASTEC/CTG EN 5

Blake P et al. Lancet 10:373,2009

- Medyan takip 4.8 yıl
- 5 yıllık sağkalım → %84
  → %84
- 5 yıllık hastalıksız sağkalım → %90
  → %89 p=0.77
- İzole vajinal-pelvik yineleme → %3
  → %6
- Akut toksisite → %57 derece 3-4 (%3 - %1)
  → %27
- Geç toksisite → %61 derece 3-4 (%8-%3)
  → %45

Erken evre çalışmalarından çıkarım!

- RT lokal kontrol avantajı sağlıyor
- Sağkalıma katkısı yok

Hasta seçimi dikkatli yapılmalı

Özellikle erken evre yüksek riskli olgularda RT uygulanmalı

Diğer olgular için daha az toksik olması nedeniyle **brakiterapi** yeterli

Eksternal RT – İntrakaviter RT karşılaştırılması
1 randomize çalışma- PORTEC II

- Orta-yüksek riskli 427 olgu
- TAH+BSO lenf bezi disseksiyonu yok
- Randomizasyon
  → 46 Gy eksternal RT
  ↘ 21 Gy intrakaviter RT
- Medyan takip 3.8 yıl
- 5 yıllık sonuçlar Lancet de yayınlandı

PORTEC II

Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial

R A Nout, V T H B M Smit, H Putter, I M Jürgenliemk-Schulz, J J Jobsen, L C H W Lutgens, E M van der Steen-Banasik, J W M Mens, A Slot, M C Stenfert Kroese, B N F M van Bunningen, A C Ansink, W L J van Putten, C L Creutzberg, for the PORTEC Study Group

- **5 yıllık vajinal yineleme**
  - ERT %1.6
  - BT %1.8
- **Lokal bölgesel yineleme**
  - ERT %2.1
  - BT %5.1
- **Uzak metastaz**
  - ERT %5.7
  - BT %8.3
- **Sağkalım**
  - ERT %85
  - BT %80
- **Komplikasyon (derece 1-2)**
  - ERT %54
  - BT %13

- **Sonuç:** vajinal brakiterapi etkin ve daha az toksik tedavi yöntemi

Yüksek risk ve/veya İleri evre olgular

- Evre IB (FIGO 2009), grade 3
- Evre II-III
- Myometrial invazyonu olan clear cell ya da seröz kanserler

Yüksek uzak metastaz riskine sahip olup bu olgularda giderek artan oranlarda ***Radyoterapi ile Kemoterapi*** birlikte kullanımı gündeme gelmektedir

Endometrium kanserinde RT-KT randomize çalışmalar

Table 2 Randomized studies on adjuvant therapy in endometrial cancer

Reference	Study population	Control arm, *n*	Experimental arm, *n*	Outcome
Randall et al. [32]	Stage III–IV of any histology, no postoperative tumor >2 cm without hematogenous or inguinal lymph node metastases	*n*=202; Whole abdominal XRT 30 Gy + pelvic ± PA boost 15 Gy	*n*=194; A 60 mg/m^2+ P 50 mg/m^2 every 3 weeks × 8 + P 50 mg/m^2 × 1	5-year OS adjusted for stage Control arm 42% Experimental arm 55% 5-year PFS adjusted for stage Control arm 38% Experimental arm 50%
Morrow et al. [34]	Stage I–II (occult) all grades, and ≥1 of: ≥50% MI, PLN+ or PAN+, cervical invasion (occult), adnexal metastases	*n*=89; Pelvic XRT 50 Gy ± PA XRT	*n*=92; XRT + A 45 mg/m^2 to maximal cumulated dose 400 (500) mg	5-year OS about 60% in both arms
Maggi et al. [35]	Stage IC grade 3 or stage IIA–B grade 3 with ≥50% MI or stage III Non-serous, non–clear cell carcinoma	*n*=166; Pelvic XRT 45–50 Gy ± PA XRT 45 Gy	*n*=174; C 600 mg/m^2 + A 45 mg/m^2 + P 50 mg/m^2 every 4 weeks × 5	5-year OS Control arm 69% Experimental arm 66% 5-year PFS Control arm 63% Experimental arm 63%
Susumu et al. [36]	Stage IC–IIIC endometrioid carcinoma ≥50% MI <75 years old	*n*=192; Pelvic XRT 45–50 Gy ± PA XRT ± VBT	*n*=193; C 333 mg/m^2 + A 40 mg/m^2 + P 50 mg/m^2 every 4 weeks × ≥3	5-year OS Control arm 85% Experimental arm 87% 5-year PFS Control arm 84% Experimental arm 82%
Hogberg et al. [37]	Stage I–III endometrioid carcinoma with ≥1 of grade 3, ≥MI, or DNA non-diploidy Stage I–III serous/clear cell carcinoma	*n*=267; Pelvic XRT ≥44 Gy ± VBT	*n*=267; Pelvic XRT ≥44 Gy ± VBT + A 50 mg/m^2 or E 75 mg/m^2 + P 50–75 mg/m^2 (83%) or other regimens in 17% every 3–4 weeks × 3–4 (1/3 had chemotherapy before XRT)	5-year OS Control arm 75% Experimental arm 82% 5-year PFS Control arm 69% Experimental arm 78%
Kuoppala et al. [38]	Stage IA–B grade 3 or stage IC–IIIA grade 1–3	*n*=72; Pelvic XRT 28 Gy in 2 courses with 3 weeks' pause between	*n*=84; C 500 mg/m^2 + E 60 mg/m^2 + P 50 mg/m^2 course 1 + pelvic XRT 28 Gy + chemo course 2 + pelvic XRT 28 Gy + chemo course 3	5-year CSS Control arm 85% Experimental arm 82%

A doxorubicin; *C* cyclophosphamide; *CSS* cancer-specific survival; *E* epirubicin; *OS* overall survival; *P* cisplatin; *PA* para-aortic; *PAN+* metastatic para-aortic nodes; *PFS* progression-free survival; *PLN+* metastatic pelvic lymph nodes; *VBT* vaginal brachytherapy; *XRT* external radiotherapy

GOG 34 (Morrow et al 1990)

GOG tarafından düzenlenmiş ilk randomize çalışma

- 1977-1986 yılları
- 224 olgu
- Evre I-II

Aşağıdaki bir ya da daha fazla risk faktörü içerecek:

- >%50 invazyon
- pelvik-paraaortik met
- servikal yayılım
- adneksiel yayılım

- Tüm olgular TAH + BSO
- 50 Gy eksternal RT sonrasında

kemoterapi (doxo)

takip

Çalışma sonucu iki grup arasında fark yok

Ancak çalışma hasta takibi, KT uygulaması açısından yetersiz ve güvenilirliği düşük olarak yorumlanmış

İtalyan çalışması (Maggi R et al. 2006)

- 1990-1997 yılları arasında
- 345 olgu

  Evre IC Gr III

  Evre IIA-B Gr III

  Evre III
- TAH + BSO+ selektif PPLÖ

KT (6 kür CAP)

RT (45-50 Gy)

- Medyan takip 96 ay

  RT kolunda %38 yineleme

  KT kolunda %42 yineleme

- Hastalıksız ve genel sağkalım fark yok

  5 yıl hastalıksız sağkalım RT %63

  KT %63

  5 yıl genel sağkalım RT %69

  KT %66

Sonuç: 2 tedavinin birlikte kullanımı araştırılmalıdır!!

GOG 122

- Tam cerrahi yapılmış evre III ve
- Abdomende sınırlı olan , <2 cm rezidüel tümör kalmış evre IV hastalar

Randomizasyon

- RT ⟶ tüm batın 30 Gy/20 fraksiyon ve
  pelvise ek doz 15 Gy

- KT ⟶ doxo (60mg/m2) ve sisplatin (50 mg/m2)
  7-8kür

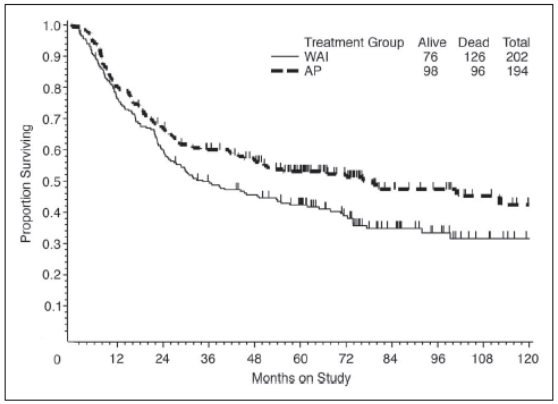


Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

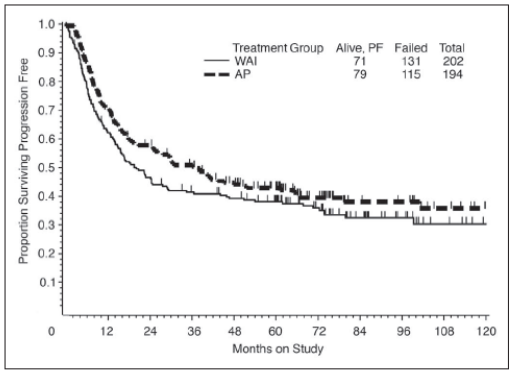


Fig 1. Progression-free survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation; PF, progression free.

Table 6. Multiple Regression Analysis

Prognostic Factor	Progression-Free Survival		Overall Survival	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Treatment, AP *v* WAI	0.67*	0.52 to 0.87	0.69*	0.53 to 0.89
Stage, IV *v* III	2.29*	1.68 to 3.11	1.90*	1.36 to 2.66
Residual disease, gross *v* microscopic	1.82*	1.26 to 2.63	1.26	0.85 to 1.86
Age, 70 *v* 60 years†	1.25*	1.08 to 1.45	1.29*	1.10 to 1.51
Race, black *v* all others	1.94*	1.41 to 2.66	1.63*	1.16 to 2.28
Cell type				
Serous *v* all others	1.39*	1.01 to 1.91	1.56	1.13 to 2.16
Clear cell *v* all others	0.65	0.33 to 1.26	0.80	0.41 to 1.55
Grade				
2 *v* 1	1.39	0.83 to 2.32	1.79	0.99 to 3.23
3 *v* 1	2.24*	1.37 to 3.68	2.45*	1.37 to 4.36
Cytology, positive *v* all others‡	1.18	0.89 to 1.55	1.32	0.99 to 1.75

Abbreviations: AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.
*$P < .05$.
†Model included both linear and quadratic terms; age terms were tested jointly. The coefficients for the age and age^2 terms in the model for progression-free survival are −0.00759 and 0.0002288, respectively. The coefficients for the age and age^2 terms in the model for overall survival are −0.00161 and 0.0002086, respectively.
‡Included one patient with missing cytology report.

GOG 122

- Pelvik yineleme

RT kolunda %21

KT kolunda %26

  - Uzak metastaz

RT kolunda %18

KT kolunda %10

(bu bulgulardan yola çıkarak GOG 184 çalışmasında KT'ye toksisiteyi de azaltmak amacıyla limited-volume RT eklenmiş)

Japon çalışması (Susumu N et al. 2008)

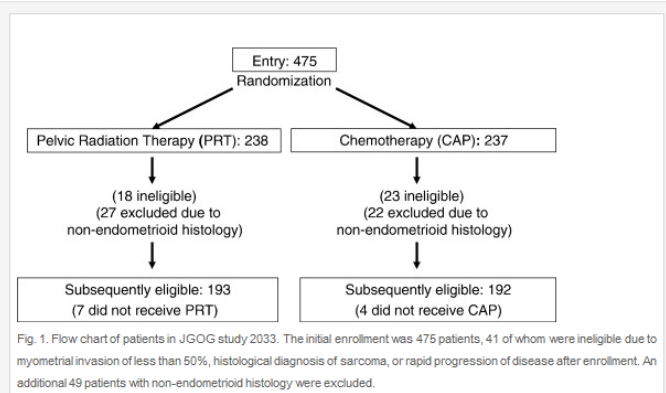


Fig. 1. Flow chart of patients in JGOG study 2033. The initial enrollment was 475 patients, 41 of whom were ineligible due to myometrial invasion of less than 50%, histological diagnosis of sarcoma, or rapid progression of disease after enrollment. An additional 49 patients with non-endometrioid histology were excluded.

- 385 olgu
- 1994-2000 yılları

  evre IC-IIIC

  < 75 yaş

  TAH+BSO uygulanmış rezidüel tm yok

  pelvik lenfadenektomi %96

RT (45-50 Gy) %3 braki

KT (CAP 3 ya da daha fazla)

- Medyan takip 60 ay

- Tedavi olguların %99 tarafından tamamlanmış

- Derece 3-4 toksisite

  RT %2

  KT %5

5 yıllık progresyonsuz sağkalım

  RT %84

  KT %82 p=0.726

5 yıllık sağkalım

  RT %85

  KT %87 p=0.208

Japon çalışması sonuçları -subgrup analizi

Table 3. Sites of initial recurrence

Recurrence sites[□]	PRT *n* = 193	CAP *n* = 192
Pelvis	11	5
Vagina only	2	9
Intrapelvic recurrence	13 (6.7%)	14 (7.3%)
Peritoneal cavity	2	2
Liver	3	1
Lung	11	15
Paraaortic lymph node	3	10
Others	7	3
Extrapelvic recurrence	26 (13.5%)	31 (16.1%)
Total recurrent cases	30 (15.5%)	33 (17.2%)

□Including multiple recurrence.CAP: cyclophosphamide, doxorubicin, and cisplatin.PRT: pelvic radiation treatment.

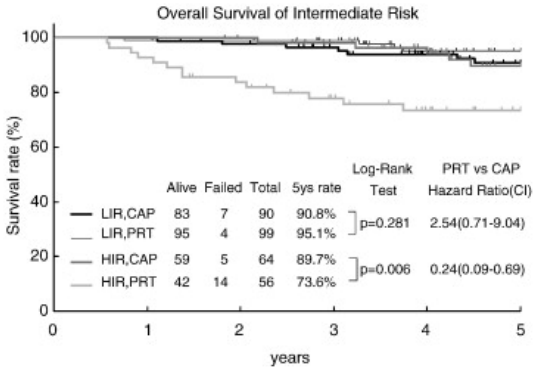


Fig. 5. Overall survival rates of intermediate risk in the PRT (pelvic radiation treatment) group and CAP (cyclophosphamide, doxorubicin, and cisplatin) group. Low–intermediate risk (LIR) was defined as stage IC patients under 70 years of age and with G1/2 endometrioid adenocarcinoma. High–intermediate risk (HIR) was defined as (1) stage IC patients over age 70 years or having G3 endometrioid adenocarcinoma or (2) stage II or IIIA (positive cytology) patients with deeper than 50% myometrial invasion in the corpus. Among LIR patients, OS rates at 5 years in the PRT and CAP groups were not statistically different. However, among HIR patients, the CAP group had significantly higher OS rate.

NSGO 9501/EORTC 55991
Hogberg et al-Eur J Cancer-2010

- Son yıllarda yayınlanan en geniş randomize çalışma
- 1996-2007 yılları
- 382 olgu
- Evre I,II,III (sadece pelvik lenf bezi (+))
- TAH+BSO uygulanmış
- Medyan takip 4.3 yıl

- Yalnız RT ile KT+RT karşılaştırılmış
- Çeşitli KT şemalarını içeriyor
- Sağkalım farkı yok RT %74

  KT %82 (p=0.08)
- Ancak KT eklenmesi ile progresyonsuz sağkalım farkı var RT %72

  KT %79 (p=0.03)

Sonuç: KT+RT etkin tedavi

EUROPEAN JOURNAL OF CANCER 46 (2010) 2422–2431

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Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer – Results from two randomised studies

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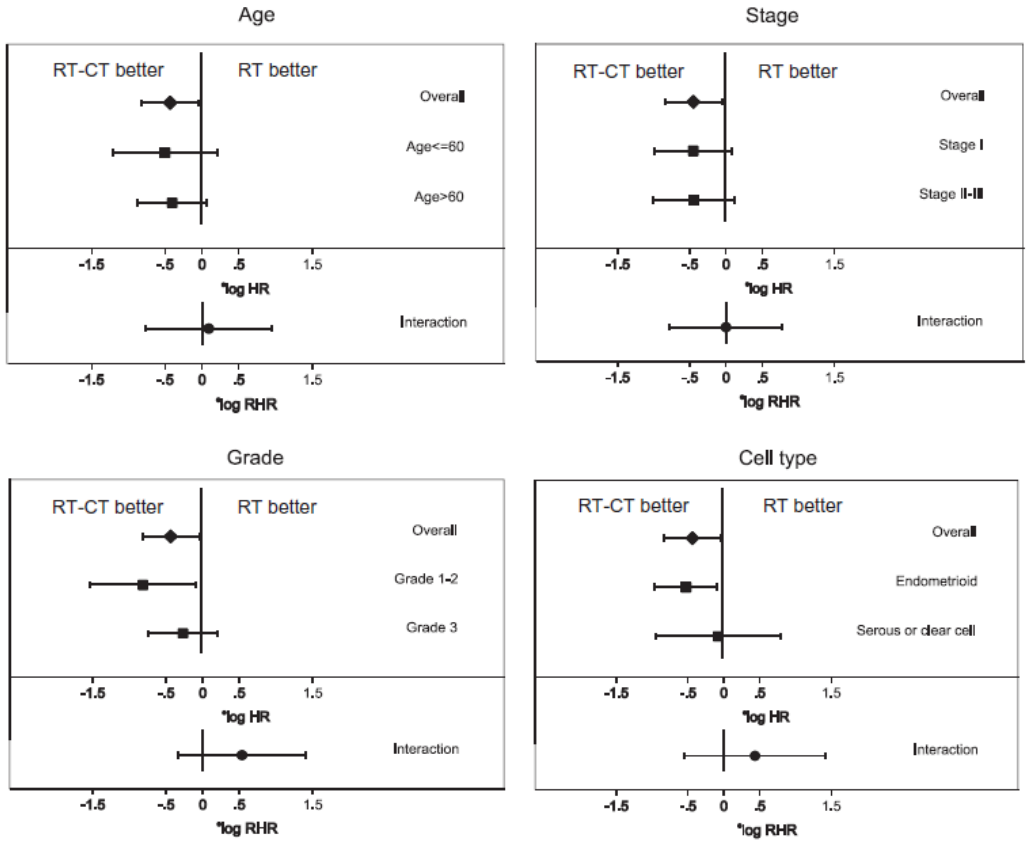


Table 3 – Results of survival analyses in different groups.

End-point	Events					HR	95% CI	P	5-Year probability of survival	
	RT	%	RT–CT	%	Total				RT	RT–CT
NSGO-EC-9501/EORTC-55991 (RT n = 191, RT–CT n = 187)										
PFS	50	26	35	19	85	0.64	0.41–0.99	0.04	0.72	0.79
OS	40	21	28	15	68	0.66	0.40–1.08	0.10	0.76	0.83
CSS	34	18	19	10	53	0.51	0.28–0.90	0.02	0.79	0.88
MaNGO ILIADE-III (RT n = 76, RT–CT n = 80)										
PFS	26	34	18	23	44	0.61	0.33–1.12	0.10	0.61	0.74
OS	17	22	14	18	31	0.74	0.36–1.52	0.41	0.73	0.78
CSS	15	20	11	14	26	0.65	0.30–1.44	0.29	0.76	0.82
POOLED NSGO-EC-9501/EORTC-55991 + MaNGO ILIADE-III (RT n = 267, RT–CT n = 267)										
PFS	76	28	53	20	129	0.63	0.44–0.89	0.009	0.69	0.78
OS	57	21	42	16	99	0.69	0.46–1.03	0.07	0.75	0.82
CSS	49	18	30	11	79	0.55	0.35–0.88	0.01	0.78	0.87
NSGO-EC-9501/EORTC-55991 endometrioid carcinoma (RT n = 115, RT–CT n = 120)										
PFS	29	25	19	16	48	0.50	0.27–0.95	0.03	0.73	0.83
OS	25	22	15	13	40	0.55	0.28–1.09	0.08	0.75	0.86
CSS	22	19	11	9	33	0.42	0.19–0.93	0.03	0.76	0.92
NSGO-EC-9501/EORTC-55991 serous and clear cell carcinoma (RT n = 76, RT–CT n = 64)										
PFS	21	28	16	25	37	0.83	0.42–1.64	0.59	0.71	0.72
OS	15	20	13	20	28	0.94	0.42–2.08	0.88	0.78	0.77
CSS	12	16	8	13	20	0.71	0.26–1.90	0.49	0.82	0.85
POOLED NSGO-EC-9501/EORTC-55991 + MaNGO ILIADE-III endometrioid carcinoma (RT n = 187, RT–CT n = 197)										
PFS	54	29	35	18	89	0.53	0.34–0.83	0.005	0.69	0.80
OS	41	22	27	14	68	0.60	0.36–1.00	0.05	0.74	0.84
CSS	36	19	21	11	57	0.51	0.29–0.91	0.02	0.77	0.87

Abbreviations: CI: confidence interval, CSS: cancer-specific survival, HR: hazard ratio, OS: overall survival, PFS: progression-free survival, R radiotherapy and RT–CT: sequential radiotherapy and chemotherapy.

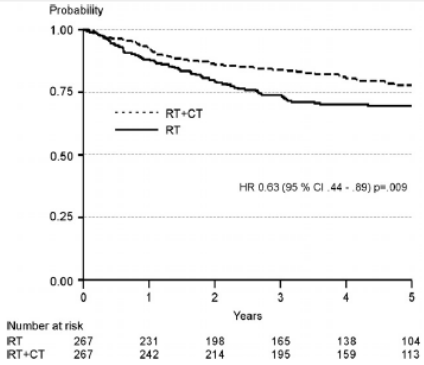
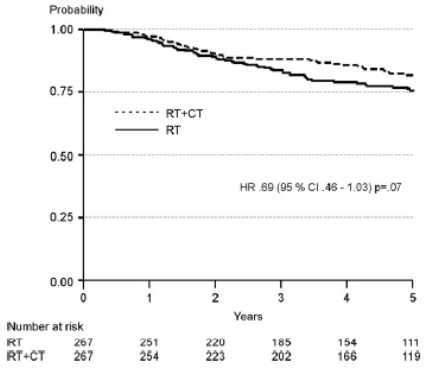


Fig. 2 – Progression-free survival in the pooled NSGO-EC-9501/EORTC-5591 and MaNGO studies (CI: confidence interval, HR: hazard ratio, RT: radiotherapy and RT–CT: sequential radiotherapy and chemotherapy).



RTOG 9708 (Greven K et al-2006 Faz II çalışma)

- Grade 2-3 ve >%50 invazyon, servikal stromal invazyon
- Pelviste sınırlı ekstrauterin hastalık

Tedavi şeması

45 Gy RT (eşzamanlı 1. ve 28. günlerde sisplatin-50 mg/m2)+braki
→ 4 kür cisplatin+paclitaxel

Çalışma sonucu

Bu uygulamanın lokal bölgesel hastalık kontrolü için etkin ,

uzak metastazları önleyici olduğu randomize çalışmalarla test edilmesi gerekliliği vurgulanmıştır

RTOG 9708

- Medyan takip 4.3 yıl
- Geç toksisite
  - Grade 1 %16
  - Grade 2 %41
  - Grade 4 %5
- Pelvik bölgesel uzak met

  %2 %2 %16
- Genel sağkalım %85
- Hastalıksız sağkalım %81

PORTEC III randomize çalışması

- 800 hasta
- Aşağıdaki kriterlerden biri ya da daha fazlasına sahip
  - evre IB grade 3 ve lenfovasküler invazyon
  - evre IC-IIA grade 3
  - evre IIB,IIIA-IIIC
  -evre IB-III seröz-clear cell

- TAH+BSO
- rezidüel tm yok

- Randomizasyon

→ Eksternal RT

→ Eksternal RT + 6 kür KT (2 kür RT ile eşzamanlı)

- Hedef:

  genel-hastalıksız sağkalım

  toksisite

  yaşam kalitesi

- Bütün bu çalışmalar
  - Kemoradyoterapi mi?
  - KT sonrası eksternal RT mi?
  - Eksternal RT + brakiterapi mi?
  - Yalnız KT ya da RT'mi?

Sorularını cevaplamak için yetersiz.....

Çok sayıda çalışma var.....

Ancak farklı RT protokolleri farklı tedavi volümleri içermekte

(Tüm abdomen RT,Pelvik-paraaortik RT,brakiterapi)

En iyi sonuçlar KT-RT birlikteliğinde

All staging in guideline is based on updated 2009 FIGO staging. (See ST-1)

CLINICAL FINDINGS	HISTOLOGIC GRADE/ADJUVANT TREATMENT[b,n,p]		
	G1	G2	G3
Completely surgically staged: Stage II[q,r] →	Vaginal brachytherapy and/or pelvic RT	Pelvic RT + vaginal brachytherapy	Pelvic RT + vaginal brachytherapy ± chemotherapy[o,p] (category 2B for chemotherapy)
Completely surgically staged: Stage IIIA →	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy	Chemotherapy ± RT or Tumor-directed RT ± chemotherapy or Pelvic RT ± vaginal brachytherapy

[b] See Principles of Radiation Therapy (UN-A).

[n] Adjuvant therapy determinations are made on the basis of pathologic findings.

[o] The role of adjuvant chemotherapy in invasive high-grade uterine confined disease is the subject of current studies. (Creutzberg, CL Clinical Trial: Chemotherapy and Radiation Therapy Compared With Radiation Therapy Alone in Treating Patients With High-Risk Stage I, Stage II, or Stage III Endometrial Cancer; Clinical trial summary from the National Cancer Institute's PDQ® database. Study ID Numbers: CDR0000521447; CKTO-2006-04; ISRCTN14387080; CKTO-PORTEC-3; EU-20664--- http://clinicaltrials.gov/ct/show/NCT00411138;jsessionid=2309E60C1051E921B4E2614F2BE708A4?order=9. Hogberg T, Signorelli M, de Oliveira CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer--results from two randomised studies. Eur J Cancer 2010;46(13):2422-2431.)

[p] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).

[q] Observation or vaginal brachytherapy is also an option for patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease.

[r] The adverse fundal risk factors influencing therapy decisions for stage I disease (see ENDO-4) may also impact the choice of adjuvant therapy for stage II disease.

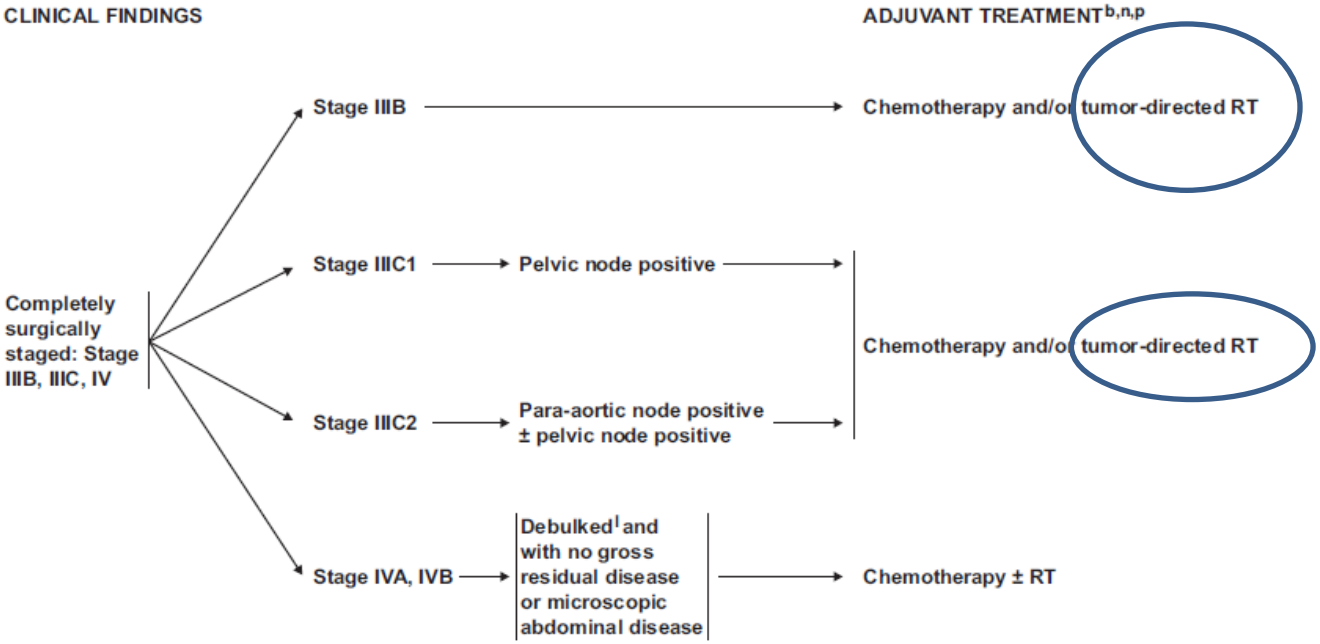
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

See Surveillance (ENDO-8)

NCCN Guidelines Version 2.2012
Endometrial Carcinoma

NCCN Guidelines Index
Uterine Neoplasms TOC
Discussion

All staging in guideline is based on updated 2009 FIGO staging. (See ST-1)



[b] See Principles of Radiation Therapy (UN-A).
[l] The surgical goal is to have no measurable residual disease.
[n] Adjuvant therapy determinations are made on the basis of pathologic findings.
[p] See Systemic Therapy for Recurrent, Metastatic, or High-Risk Disease (ENDO-B).

See Surveillance (ENDO-8)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Düşük risk Orta risk Yüksek risk

Yaş Myometrial invazyon Evre

Cerrahi histolojik grade lenfovasküler invazyon

Yan etki

hastanın genel durumu

Tüm kanserlerde olduğu gibi tedavi kişiselleştirilmeli

Yeni çalışmalara ihtiyaç var

Yürümekte olan çalışmalar

Ongoing trials	Planned no.	Randomization	Accrual January 2011
PORTEC-3	670 Stages I–III with high-risk factors; serous/cc	Pelvic RT vs RT-CT (2× C during RT and 4× TC)	300
GOG#249	562 Stages I–II with high-risk factors or serous/cc	Pelvic RT vs VBT and CT (3× TC)	175
GOG#258	804 Stages III/IV	RT-CT (2× C during RT and 4× TC) vs CT (6× TC)	132

A doxorubicin; *AP* doxorubicin/cisplatin; *CAP* cyclophosphamide/doxorubicin/cisplatin; *CEP* cyclophosphamide/epirubicin/cisplatin; *CT* chemotherapy; *ns* not statistically significant; *RT* radiation therapy; *TAP* paclitaxel/doxorubicin/cisplatin; *TC* paclitaxel/carboplatin; *TEP* paclitaxel/epirubicin/cisplatin; *WART* whole abdominal radiotherapy

Sonuç

- Erken evrede RT lokal kontrol avantajı sağlıyor, sağkalıma katkısı yok
- Brakiterapi ve IMRT teknikleriyle daha az yan etki – yüksek lokal kontrol sağlanabilir
- Özellikle yüksek riskli ve/veya ileri evre endometrium kanserli olguların tedavisinde Kemoterapi önemli bir yer tutmakta
- Yapılan çalışmalardan çıkarım RT-KT birlikte kullanımı ile sağkalım oranlarının arttığı yönünde

Teşekkürler