LOKAL İLERİ SERVİKAL KANSER YÖNETİMİ

Doç Dr Ahmet Barış GÜZEL
ÇÜTF Kadın Hastalıkları ve Doğum AD
ADANA

Evreleme FIGO 2009

Erken Evre

↓

Ia1, Ia2, Ib1 and IIa1

İleri Evre

↓

Ib2, IIa2 ve diğer

Serviks Kanseri erken evre tanısı %20-25

Pecorelli S. , Int J Gynecol Obstet, 2009

Lokal İleri Servikal Kanser

Evre 1b2 - 4a (2a1 hariç)

Evre 2b - 4a

Sadece cerrahi ile başarılı şekilde (%85 kür oranı ile) tedavi edilecek boyutu aşmış tümörler*

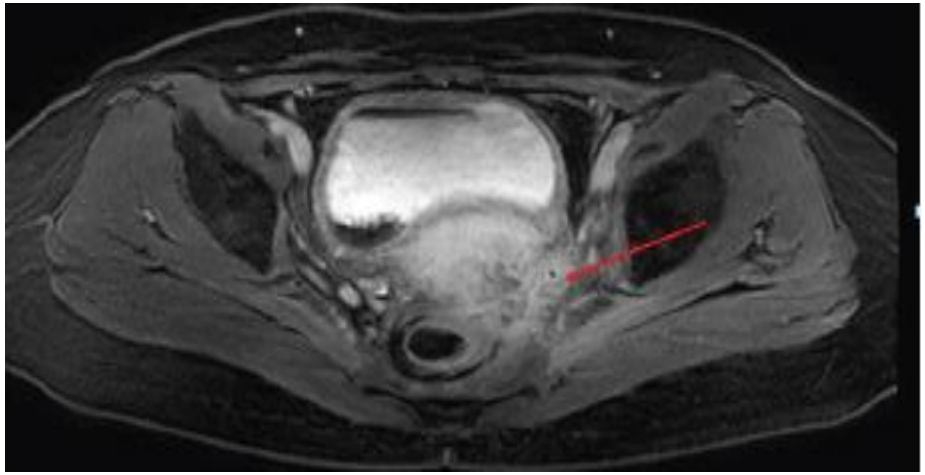
*Rose PG. Curr Opin Obstet Gynecol 2001

Tedavi Sonuçları

Evre	Primer tedavi	5y GS (%)
IB2-IIA	RT	80
IIB	RT	65-75
III	RT	30-50
IVA	RT	10-15
IVB	KT, palyatif RT	0

Lokal İleri Servikal Kanser

- Yüksek rekürrens oranları
- Kötü survi



PREOPERTİF KLİNİK DEĞERLENDİRME

Yöntemler	Uygunluk %	Sensitivite %	Spesifite %
Lenfanjiyografi	28-83	47-100	85
USG	82-90	55-82	76-94
CT	(>2 cm LN) 55-85	56-84	76-93
MRI	(>1.5 cm LN) 75-84	31-38	75-84
FNA	68-82	58	65
PET	75-85	10-92	75-96

Chou HH, 2006; Follen M, 2003; Ozsarlak O, 2003; Hansen, 2000; Goff BA, 1999; Rose PG, 1999; Heaps JM, 1990

KLİNİK EVRELEMEDE PET

Otör	n	+PET/+Pat	Sensitivite
Chou HH	60	1/10	10%
Wright JD	59	13/31	36%
Lin WC	50	12/14	86%
Yeh LS	42	10/12	83%
Reinhardt MJ	35	10/11	91%
Rose PG	32	6/8	75%
Narayan K	24	4/7	57%

Chou HH, 2006; Wright JD, 2005; Lin WC, 2003; Yeh LS,, 2002; Reinhardt MJ, 2001; Rose PG, J 1999; Narayan K, 2001

Table 1. Comparison of the Available Parameters for CT, MRI and PET/CT for Locoregional Disease Evaluation

	CT					MRI					PET/CT				
	Sens	Spec	PPV	NPV	Acc	Sens	Spec	PPV	NPV	Acc	Sens	Spec	PPV	NPV	Acc
Primary tumor visualization	93%	N/A	N/A	N/A	53%	93%	N/A	N/A	N/A	86-93%	91-100%	N/A	91%	N/A	N/A
Parametrial invasion	43-55%	71%	53%	62%	59-72%	52-80%	63-91%	55-67%	61-95%	58-95%	N/A	N/A	N/A	N/A	N/A
Bladder invasion	64-100%	73-92%	40%	100%	92%	75-100%	88-91%	7%	96-100%	88-99%	N/A	N/A	N/A	N/A	N/A
Rectal invasion	45-100%	88-91%	N/A	100%	100%	71-100%	91%	17%	96-100%	91%	N/A	N/A	N/A	N/A	N/A
Lymph node metastasis	31-50%	84-92%	61%	64%	81-86%	36-89%	78-99%	64-68%	57%	67-86%	10-95%	83-100%	25-90%	84-99%	75-92%

*Sens: Sensitivity, Spec: Specificity, PPV: Positive predictive value, NPV: Negative predictive value, Acc: Accuracy, N/A: No information available.

	CT	MRI	PET/CT
Primary tumor visualization	Feasible	Recommended	Feasible
Parametrial invasion	Feasible	Recommended	-
Vaginal invasion	-	-	-
Bladder invasion	Feasible	Recommended	-
Rectal invasion	Feasible	Recommended	-
Pelvic lymph node metastasis	Feasible	Feasible	Recommended
Para aortic lymph node metastasis	Feasible	Feasible	Recommended
Distant metastasis	-	-	Recommended
Tumor response after definitive treatment	Feasible	Feasible	Recommended

Advanced Imaging Applications for Locally Advanced Cervical Cancer

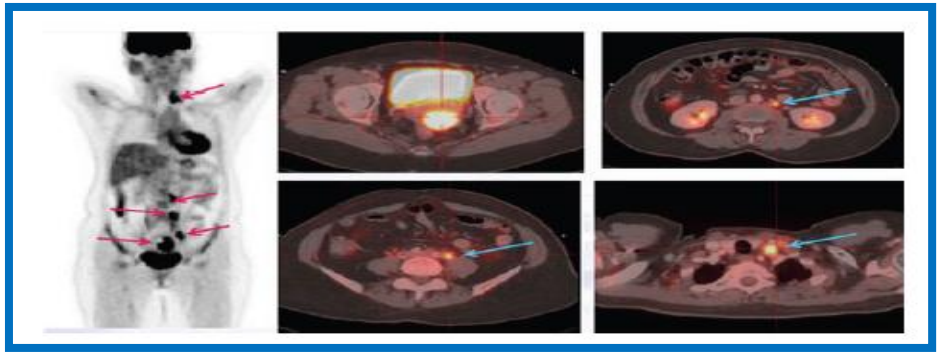
Janjira Petsuksiri[1,*], Atthapon Jaishuen[2], Pittayapoom Pattaranutaporn[1], Yaowalak Chansilpa[1]

Asian Pacific Journal of Cancer Prevention, Vol 13, 2012

In conclusion, advanced imaging has played a significant role in recent cervical cancer staging and treatment. MRI appears to be better than CT for locoregional disease assessment especially for primary tumor and adjacent soft tissue extension. PET/CT shows benefits of whole body tumor metabolic evaluation in addition to providing locoregional anatomic assessment.

Preoperatif Değerlendirme

- Preoperatif olarak lenf nodların değerlendirilmesi
- CT taramasında şüpheli olgularda Lenf nodu değerlendirlmesi
  - Lefadenektomi
  - CT eşliğinde biopsi
  - PET CT



- Preoperatif hidroüreteronefroz değerlendirilmesi
  - Obstruksiyon varsa tedavi edilmeli
    - (PFS: median 18 versus 10 months; OS median 34 versus 17 months)
    - Rose PG et al Gynocol Oncol 2010

Lokal İleri Servikal Kanserde Tedavi Seçenekleri

- **Konkomitan Kemo RT**

- **Neoadjuvan KT + cerrahi**
- **Neoadjuvan KT + RT**
- **Cerrahi + adjuvan RT**
- **Cerrahi + adjuvan KT**
- **Cerrahi + adjuvan kemo RT**
- **RT sonrası cerrahi**

Eifel PJ. Nature Clin Pract Oncol 2006 Loizzi V. Gynecol Obstet Invest 2007

Primer Kemoradyoterapi

- Küratif cerrahi yapılamayacağından primer cerrahi önerilmez
- Adjuvan tedavi gerekliliği
- Artmış morbidite
  - (%26 - %12 Yamasima H A J Clin Onc 2010)

RT / RT + KT

- Kemoterapi
  - RT hasarının onarımının inhibisyonu
  - Hücrelerde RT ye duyarlı fazda toplanma
  - Hipoksik hücrefraksiyonunun azaltılması
  - Direkt sitotoksik etki

VOLUME 26 · NUMBER 35 · DECEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration

A

Trial ID	CTRT events	CTRT pts.	Control events	Control pts.	O-E	Variance
Trials of Chemoradiation *v* radiotherapy						
(a) Platinum-based CTRT						
Onishi[44] (CDDP or CDBCA)	16	26	15	23	1.52	7.59
Pearcey[43] (CDDP)	53	130	60	129	-5.00	28.20
GOG0123[6] (CDDP)	49	185	69	189	-12.90	29.38
Chen[23] (a) (CDDP FU VCR)	8	30	8	30	0.21	4.00
Chen[23] (b) (CDDP FU VCR)	6	30	7	30	-0.45	3.25
Pras (CDBCA FU)	17	28	16	26	-0.47	8.15
GOG0165[26] (a) (CDDP)	8	26	12	24	-3.03	4.92
Cikaric[47] (CDDP)	37	100	48	100	-8.02	21.12
Leborgne (CDDP FU)	75	170	85	170	-3.07	39.91
Gariapagaoglu[48] (CDDP)	9	22	8	22	0.70	4.23
Lal[50] (CDDP)	14	94	12	86	0.62	6.49
Sub-total	292	841	340	829	-29.89	157.23
(b) Non–platinum-based CTRT						
Thomas[24] (a) (FU)	24	57	32	58	-5.16	13.83
Thomas[24] (b) (FU)	26	58	25	60	0.71	12.74
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242	-12.52	24.57
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221	0.31	25.67
Roberts[49] (MMC)	25	124	39	124	-8.39	15.92
GOG0165[26] (b) (FU)	11	27	12	24	-0.82	5.55
Sub-total	180	729	216	729	-25.87	98.28
Total	472	1,570	544	1,534	-54.56	251.54
Trials of CTRT + adjuvant chemotherapy *v* radiotherapy						
SWOG8797[8,46] (CDDP FU)	28	135	54	133	-15.61	20.36
Kantardzic[45] (CDDP BLM)	15	40	25	40	-7.74	9.74
Sub-total	43	175	79	173	-23.35	30.10

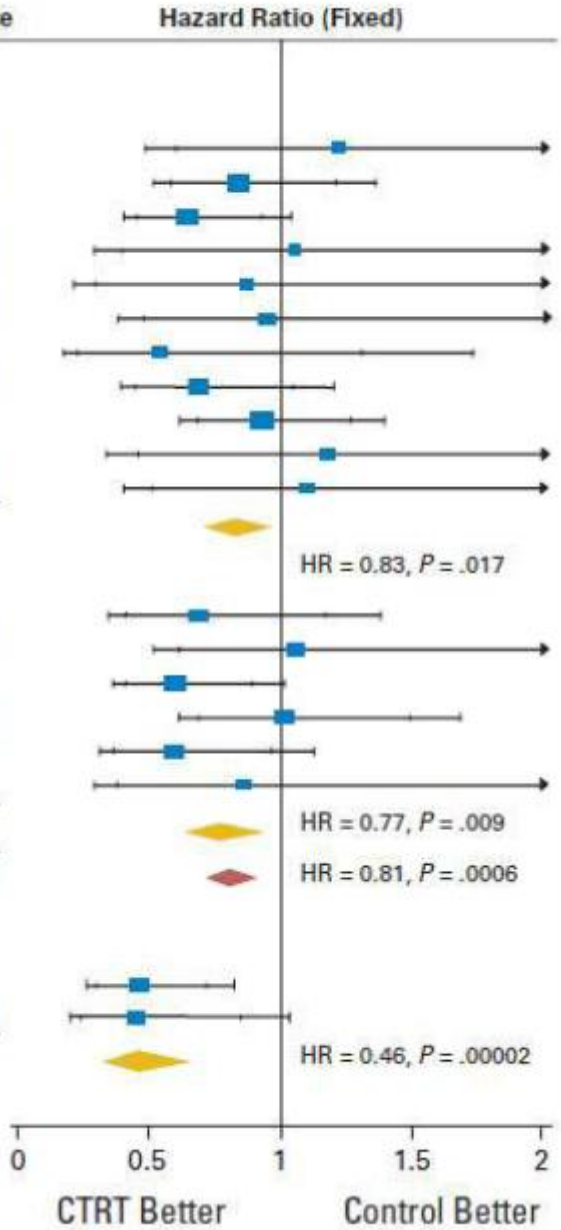


Table 3. Results of All Outcomes for the Main Analyses

Survival Measure	Main Analysis (13 trials)			
	HR	95% CI	*P*	Absolute 5-Year Survival Benefit (%)
Overall disease-free survival	0.78	0.70 to 0.87	.000005	8
Locoregional disease-free survival	0.76	0.68 to 0.86	.000003	9
Metastases-free survival	0.81	0.72 to 0.91	.0004	7
Locoregional disease-free interval	0.74	0.64 to 0.86	.00009	6
Metastases-free interval	0.83	0.71 to 0.99	.037	4

NOTE. Two trials in which additional adjuvant chemotherapy was administered on the treatment arm are excluded.

J Clin Oncol 26:5802-5812. © 2008

RT / RT Kemoterapi

- 4580 olgu 19 RKT
- Lokal kontrol ve uzak relaps açısından kemoradyasyon avantajlıdır

Green J, Kirwan J, Tierney J, *et al.* Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. Cochrane Database Syst Rev 2001:CD002225.

RT / RT Kemoterapi

- Evre IB – IIA , IIB, ve III-IVA servikal kanser, 5 yıllık survi avantajı %10,%7 ve %3 HR 0.69
- Progresyonsuz sağ kalım %13 HR 0.66
- Lokal rekürrens OR 0.59
- Uzak metastaz OR 0.8

  - Cochrane Database Syst Rev. 2010

KEMOTERAPİ REJİMLERİ

- Cisplatin (40 mg / m2)
- Cisplatin + 5 FU
  - Hematolojik toksisitede artış
  - Benzer komplet yanıt oranları
- Cisplatin + Gemsitabin
  - PFS ▲ (HR for progression 0.68, 95% CI 0.49 to 0.95; three-year PFS 74 versus 65 percent)
  - OS ▲ (OS, HR for death 0.68, 95% CI 0.49 to 0.95)
  - Toksisitede artış
  - Dueñas-González A J Clin Oncol. 2011

KEMOTERAPİ REJİMLERİ

- Data çok kısıtlı
- Carboplatin
  - Carboplatin (100 mg m2)RT / Cisplatin RT
  - Benzer yanıt
  - Benzer 3yıllık survi
  - Benzer toksisite

- Nam EJ. Comparison of carboplatin- and cisplatin-based concurrent chemoradiotherapy in locally advanced cervical cancer patients with morbidity risks. Oncologist. 2013

KEMOTERAPİ REJİMLERİ

- Gemsitabin (300 mg/m2)
  - Data çok kısıtlı
  - 9 olgu
  - 11 ay takip
  - Ciddi nötropeni,dermatit, proktit, ve kolit
    - Cetina l. Anticancer Drugs. 2004

KEMOTERAPİ REJİMLERİ

- Haftalık Paklitaksel
  - 13 olgu 8 olguda (%62) komplet yanıt
  - 5 olguda barsak toksisitesi
  - Data yeterli değil

- SONUÇ
  - Cisplatin 1. seçenek
  - Cisplatin alamayan olgularda haftalık Carboplatin

RT / Brakiterapi

- 7000 olgu evre IB2 - IVA Surveillance, Epidemiology and End Results database .
  - Kanser spesifik survi (64 / 52) ve total survi l (58 / 46 percent) 4 yıl.
- Tümör evresine ve boyutuna bağlı olarak servikal regresyon 2 – 5 haftalık tedavi ile sağlanmaktadır.

  - Han K. Trends in the utilization of brachytherapy in cervical cancer in the United States. Int J Radiat Oncol Biol Phys. 2013

Paraaortik Nodların Tedavisi

- Paraarortik nodların tutulumu kötü prognostik faktör
  - Macdonald OK Am J Clin Oncol. 2009

- CT taramasında şüpheli olgularda Lenf nodu değerlendirlmesi
  - Lefadenektomi
  - CT eşliğinde biopsi
  - PET CT
    - Uptodate 2014

Curr Oncol, Vol. 20, pp. xx-xx; doi: http://dx.doi.org/10.3747/co.20.1412

ORIGINAL ARTICLE

Positron-emission tomography for locally advanced cervical cancer: a survey assessing Canadian practice patterns and access

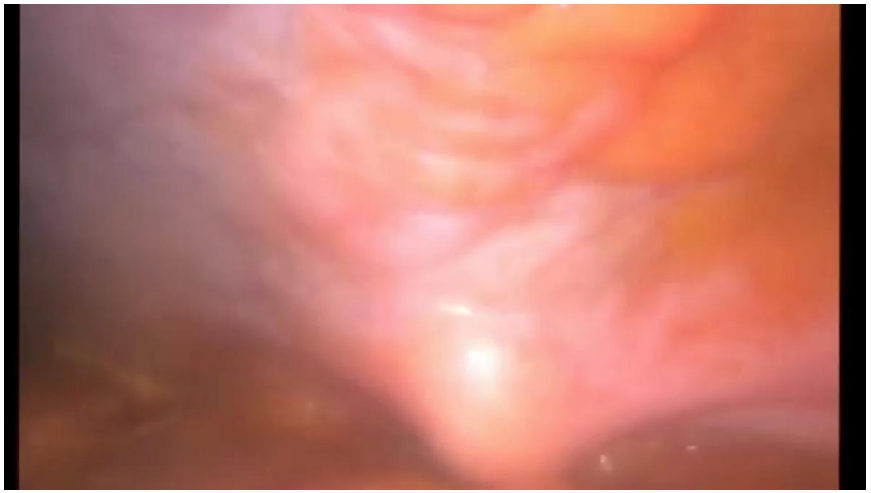
R. Banerjee MD,* *G. Dundas* MD,† *and C. Doll* MD*

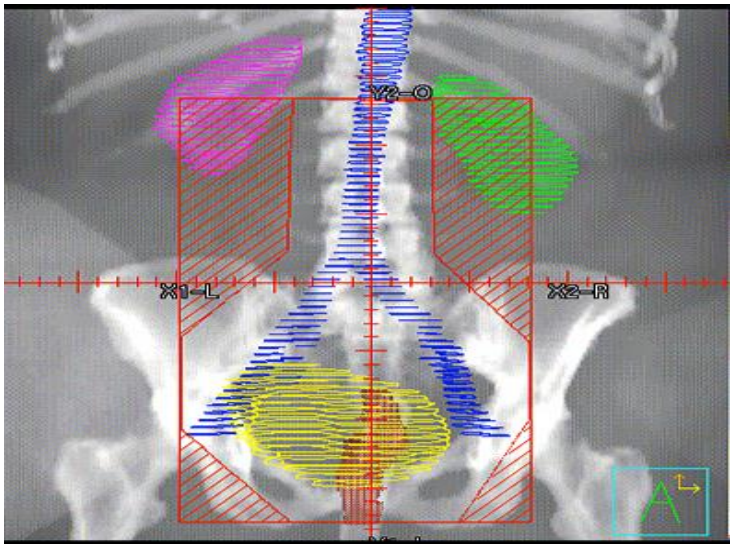
Combined PET-CT can be extremely helpful in assessing LACC patients for response to treatment. In addition to initial stage and lymph node status, post-treatment response based on PET-CT strongly predicts for disease recurrence[3]. Schwarz *et al.* prospectively

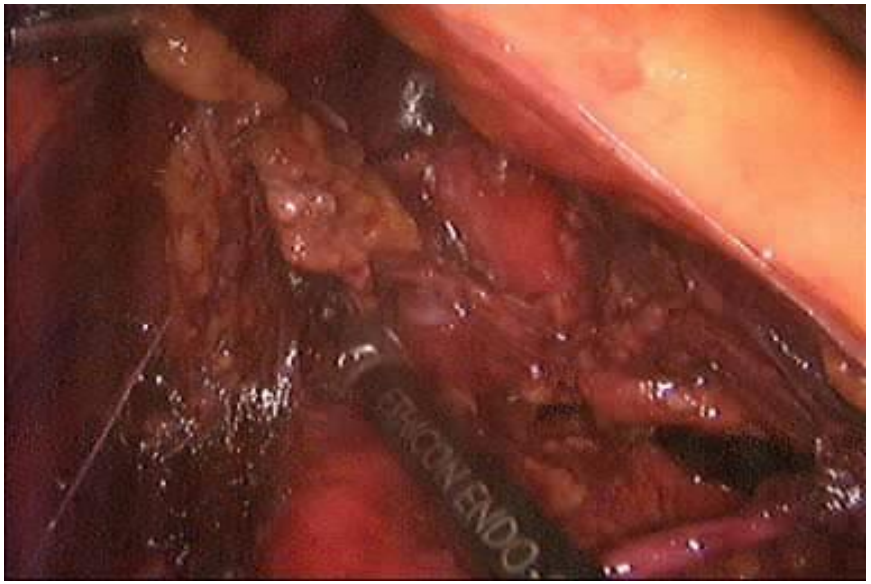
Paraaortik nodların Değerlendirilmesi

- Genişletilmiş RT (T12-L1)

Toksisiteden dolayı tutuluma dair data olmalı







Tartışmalı Konular

- Kemoradyasyon sonrası histerektomi ????
- Kemoradyasyon sonrası sistemik kemoterapi ???

	5 yıllık Lokal kontrol	Pelvik Failure	5 yıllık Survi
RT	74	26	62
RT+Hys	76	24	55

Sonuç: Bu grup hastalarda, extrafasial histerekkomi rutin değildir.

Stage IB or IIA-B carcinoma of the intact uterine cervixgreater than or equal to 6 cm in diameter: Is adjuvant extrafascial hysterectomy beneficial? Int J Radiat Oncol Biol Phys. 1991 Sep;21(4):899-904.

Kemoradyasyon Sonrası Histerektomi

- DFS VE OS Açısından anlamlı fark yok
  - Morice P. Oncologist. 2012
  - Darus CJ Int J Gynecol Cancer. 2008
- Alt uterin segment tutulumu olan 7 cm den büyük tümörlerde relapsı azaltmak için yapılabilir ???????

Kemoradyasyon Sonrası Sistemik Kemoterapi

- CP + Gemcitabin
- DFS ve OS ye katkı gösteren çalışmalar mevcut
- Artmış toksisite ile birlikte
- Kanıt düzeyi düşük

NACT

NA CT yeni seçenek olabilir mi ??

SCC kemosensitif mi ?
(Özellikle cis-platin içeren rejimler)

RT imkanlarının sınırlı olduğu ülkelerde (Asya, Güney Amerika, Avrupa'nın bir kısmı)
NA CT + cerrahi daha iyi seçenek mi ?

- Tümör volümünün azalması
- Mikrometastazların ortadan kaldırılması
- Operabilitenin artması

NACT Cerrahi

- Neoadjuvan Tedavi
  - Tümör hacminde azalma
  - Operabl hastalarda daha konservatif cerrahi
  - Daha az adjuvan tedavi
  - Subklinik metastazların ortadan kaldırılması
  - İnvivo kemosensitivitenin değerlendirilmesi
  - Genç hastalarda FSS şansı

NACT

- Neoadjuvan Tedavi
  - Toksisite
  - Definitif tedavinin gecikmesi
  - Cerrahide zorluk
  - Radyorezistans klonların gelişmesi
  - Radyoterapi ile cross rezistans

Robova H. Int J Gynecol Cancer 2010 Kumar J. Int J Gynecol Cancer 2009
Monk BJ. Clinical Gynecologic Oncology 2007 Buda A.J Clin Oncol 2005
Sardi J. Curr Opin Obstet Gynecol 2005

NACT

- Sistematik Derleme
  - Evre IB – IIIB 6RKT n =1072
  - Cisplatin bazlı rejimler 2-4 kür
  - NACT ile PFS artar OS değişmez
  - Lokal ve uzak rekürrensler ve rezektabilite oranlarında NACT lehine anlamlı olmayan fark
  - NACT Kolunda pozitif LN ve parametrium daha az

Rydzewska L, Cochrane Database Syst Rev 2010

NACT

- 2 çalışmada avantajlı gösterilse de bugün için primer tedavi kemoradyoterapidir
- Evre IB-IIA olgularda NACT cerrahi kullanılabilir

Locally advanced cervical cancer: what is the standard of care?
Zeina Al-Mansour and Claire Verschraegen

Current Opinion in Oncology 2010, 22:503–512

Cerrahi / RT KT

- Ekzenterasyon
- Sonuçlar iyi görünmekle birlikte
- Data kısıtlı, olgu sayıları yetersiz

ONCOLOGY

Exenteration as a primary treatment for locally advanced cervical cancer: long-term results and prognostic factors

Dirk Michael Forner, MD; Bjoern Lampe, MD

www.AJOG.org

TABLE 1

Characteristics of clinicopathological characteristics of the patients

Characteristic	n or median	Range
Number of patients	35	
Age, y	52	35–71
Operation time, min	442	237–685
Hospital stay, d	33	10–117
ICU stay, d	3	1–5
Anterior exenteration	17	
Posterior exenteration	2	
Total exenteration	16	
Squamous cell cancer	35	
FIGO stage		
T2	7	
T3	10	
T4	18	
Nodal status negative	15	
Pelvic lymph node metastases	14	
Pelvic and paraaortal lymph node metastases	6	
Surgical result		
R0 microscopically free of tumor	30	
R1 microscopic tumor remnants	4	
R2 macroscopic tumor remnants	1	
Grading		
G2	10	
G3	25	

FIGO, International Federation of Gynecology and Obstetrics; *ICU*, intensive care unit.

Forner. Primary exenteration for cervical cancer. Am J Obstet Gynecol 2011.

FIGURE 2

Analysis for patients without and with pelvic lymph node involvement

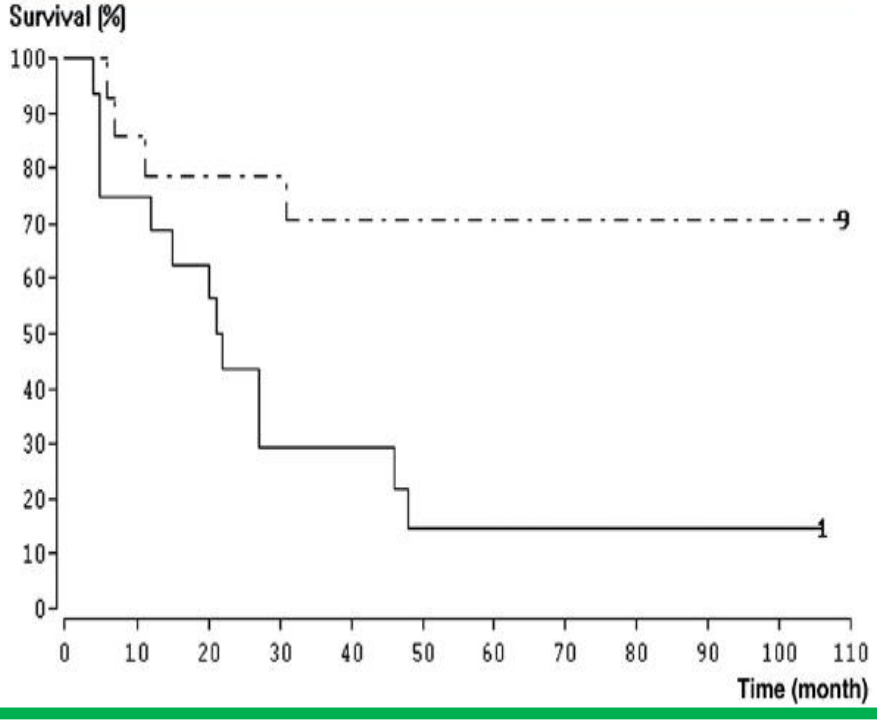
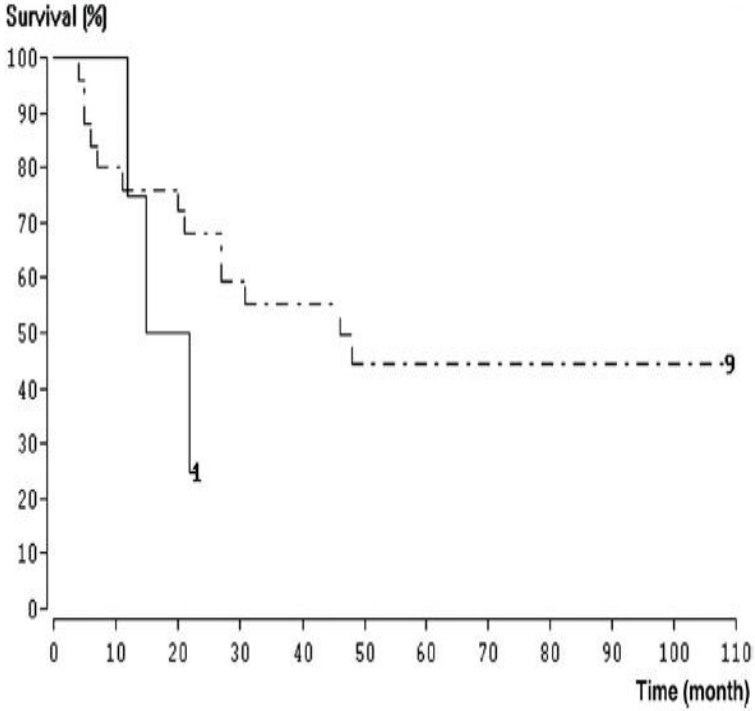


FIGURE 3

Analysis for survival relative to the degree of resection



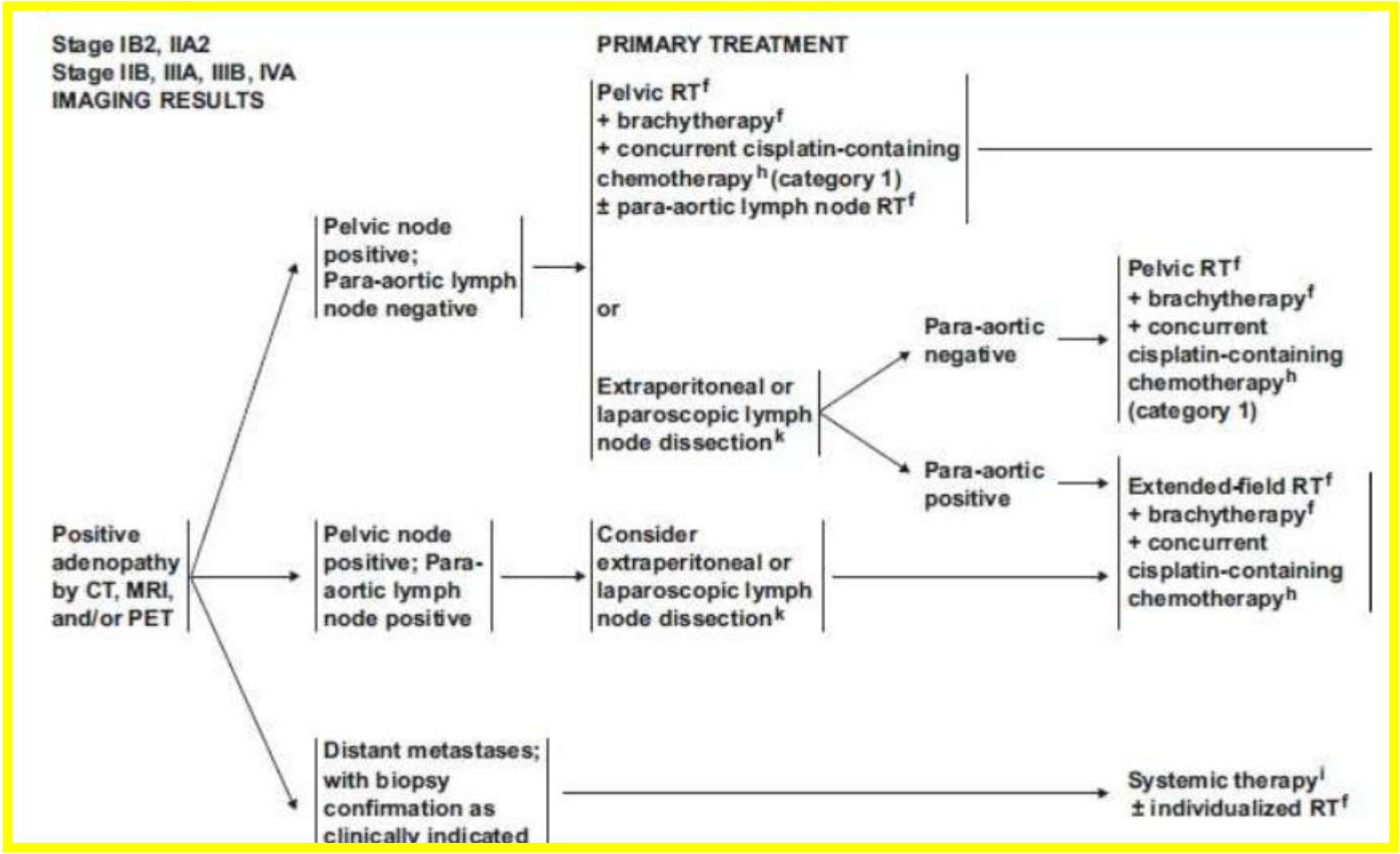
Comment

Our study shows pelvic exenteration to be a treatment option for primary LACC. The mortality for this procedure is low, and the rate of complications is acceptable, given that it is not higher than the rate of complications seen in recurrent cervical cancer or other comparable situations.[4,17,18] In our population,

Conclusion

In locally advanced cervical cancer, PE is a treatment option that yields long-term results comparable with those seen in chemoradiation and shows a comparable rate of severe complications when the tumor can be fully resected and there is no spread to lymph nodes or distant metastases. Thus far, there are no studies comparing the outcome of chemoradiation to surgery in advanced cervical cancer. The available data show that the results of exenterative surgery in primary LACC are at least equivalent to those of chemoradiation. ■

NCCN


Stage IB2, IIA2
Stage IIB, IIIA, IIIB, IVA
IMAGING RESULTS
PRIMARY TREATMENT
Positive adenopathy by CT, MRI, and/or PET
Pelvic node positive; Para-aortic lymph node negative
Pelvic node positive; Para-aortic lymph node positive
Distant metastases; with biopsy confirmation as clinically indicated
Pelvic RT[f] + brachytherapy[f] + concurrent cisplatin-containing chemotherapy[h] (category 1) ± para-aortic lymph node RT[f]
or
Extraperitoneal or laparoscopic lymph node dissection[k]
Para-aortic negative
Para-aortic positive
Pelvic RT[f] + brachytherapy[f] + concurrent cisplatin-containing chemotherapy[h] (category 1)
Consider extraperitoneal or laparoscopic lymph node dissection[k]
Extended-field RT[f] + brachytherapy[f] + concurrent cisplatin-containing chemotherapy[h]
Systemic therapy[l] ± individualized RT[f]

SONUÇ

- Primer tedavi Kemoradyoterapidir
- Preoperatif lenfnodlarının değerlendirilmesinde PETCT kullanılabilir
- PETCT de paraaortik nod pozitif olgularda lenfadenektomi yapılabilir
- Paraaortik lenf nod pozitif olgularda extended field RT verilmelidir

Sonuç

- Kemoradyoterpi sonrası histerektomi önerilmez fakat 7 cm den büyük ve alt uterin segment tutulumu olan olgularda rezidü riski yüksek olduğu için bazı otörler tarafından bu olgularda önerilmektedir.

TEŞEKKÜR EDERİM