Management of Cervical Cancer diagnosed following simple hysterectomy

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Cervical cancer Epidemiology

- The second most common gynecological cancer.
- The leading causes of cancer mortality worldwide.
- The incidence has been on the decline, occult cervical carcinomas are sometimes detected after simple hysterectomy carried out for supposedly benign gynecologic conditions or preinvasive cervical lesions.
- The incidence ranges from *5.3%* to *10.7%* of all invasive cervical cancers

Park JY, Kim DY, Kim JH, et al. Management of occult invasive cervical cancer found after simple hysterectomy. Ann Oncol.2010;21:994-1000.
Munstedt K, von Georgi R, Zygmunt M, et al. Shortcomings and deficits in surgical treatment of gynecological cancers:
a German problem only? Gynecol Oncol. 2002;86337-343.

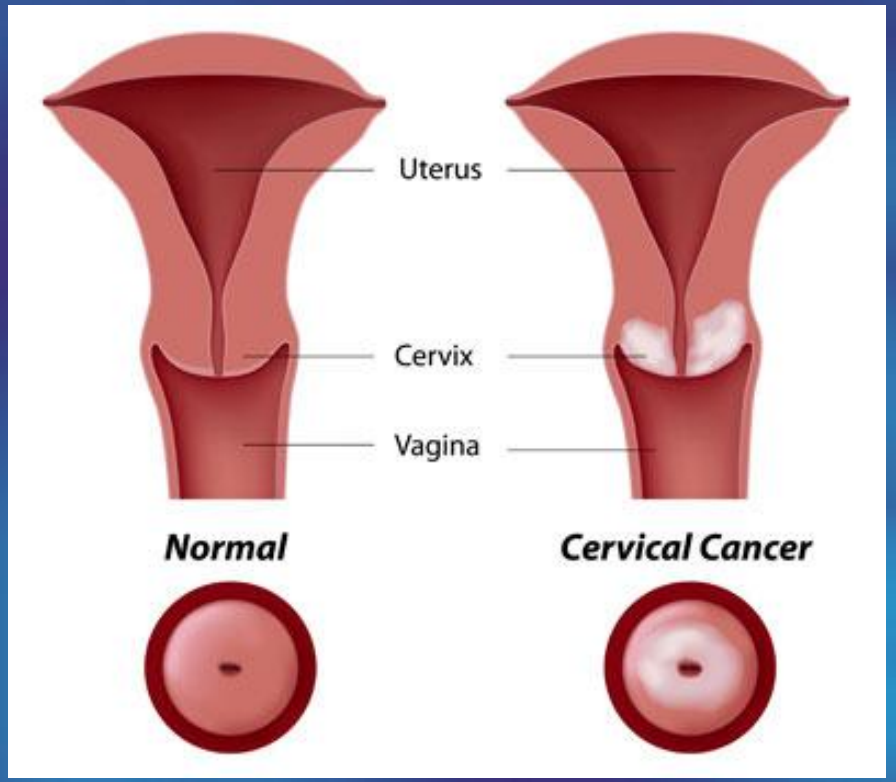
Reasons for this unfortunate condition

- Lack of preoperative PAP smear
- Failure to check cytology before the operation
- Inadequate evaluation of an abnormal cervico-vaginal smear or cervical biopsy
- Failure to perform a cone biopsy, or endocervical curettage when indicated
- Deliberate hysterectomy for grossly invasive cancer
- Errors at colposcopic examination, negative cytology, and
- No clinical evidence of cancer.

Gynecologic Oncology 94 (2004) 515–520

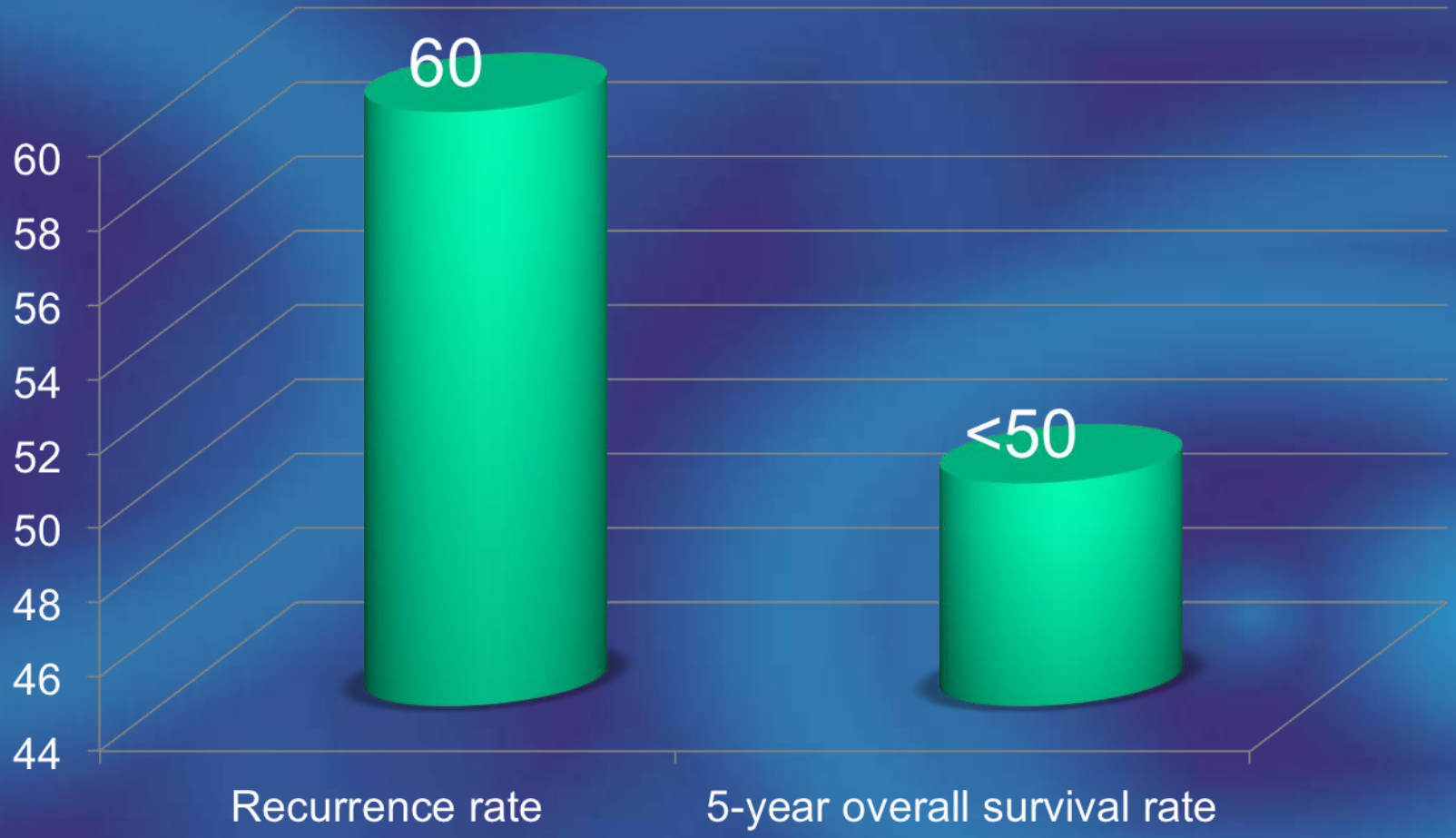
Why surprised? What is the problem?

- The problem lies in choosing the appropriate treatment modality for this rare condition.
- Limited data are available.
- Only to report conflicting results.
- No strict current guidelines for this rare condition.
- Most patients are in early stages.



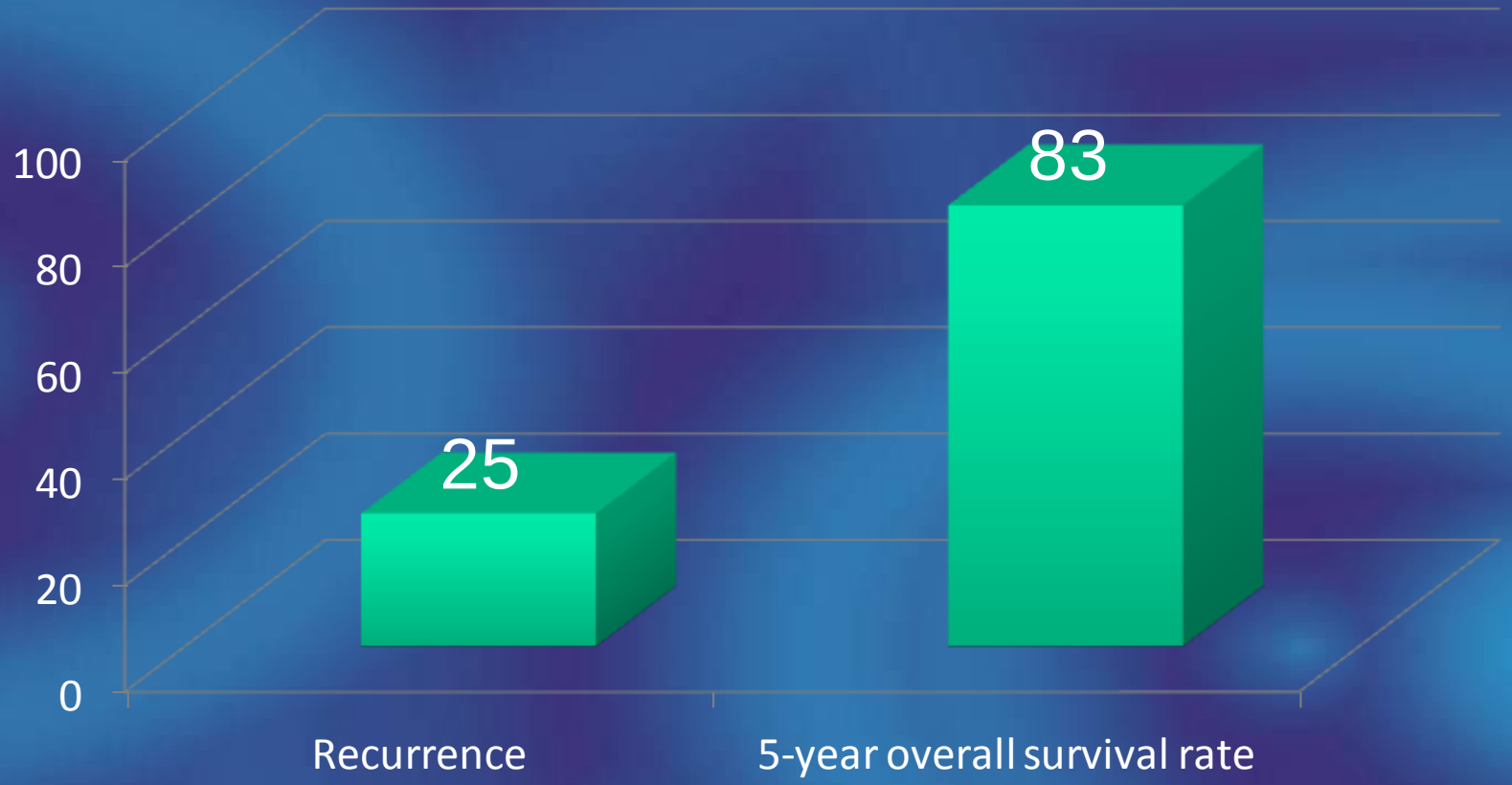
Ayhan et al, J Surg Oncol 2006

Survival and recurrence rates in suboptimal management of cervical cancer



J Low Genit Tract Dis 2004;8:102–5.
Gynecol Oncol 2008;111:18–21.

Survival and recurrence rates in optimal surgical management of cervical cancer



Lancet 1997;350:535–540

Adjuvant therapy to whom?

- Whether adjuvant treatment is required or not and what type of adjuvant treatment is best depend on her pathologic findings after SH.
- Pelvic lymph node (LN) metastasis, para-metrial invasion, and positive surgical resection margin (RM) are grouped into high-risk factors.
- A large tumor size, deep stromal invasion, and lymphovascular space invasion (LVSI) are grouped into intermediate-risk factors.

Adjuvant therapy to whom scoring system

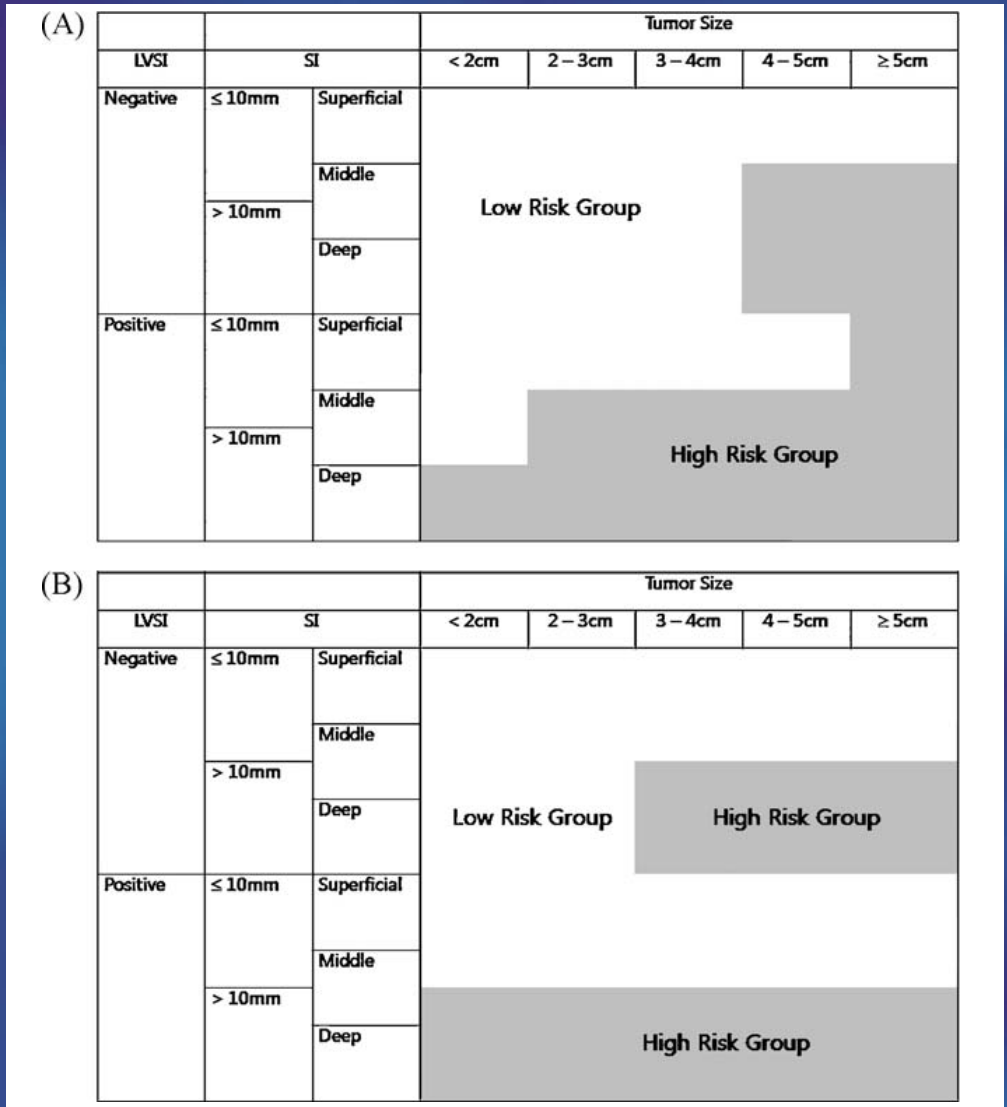


Fig. 1. High-risk groups according to combinations of intermediate-risk factors. (A) GOG criteria. (B) New criteria.

European Journal of Obstetrics & Gynecology and Reproductive Biology 147 (2009) 91–96

Adjuvant therapy to whom? Difficulties

- Parametrial invasion is difficult to evaluate precisely owing to the lack of adequate parametrial tissue in SH specimens.
- This situation makes it more difficult to decide what treatment modality to use.
- A NEW SCORING SYSTEM IS NEEDED.

Adjuvan therapy to whom? New scoring system

TABLE 1. Risk scoring system

	Score		
	1	**2**	**3**
DOI, mm	3< DOI ≤5	DOI >5	-
Tumor size, mm	7< LD ≤20	LD >20	-
LVSI	Positive	-	-
PM	-	-	Positive
RM	-	-	Positive
LN	-	-	Positive

Low-risk group: score 1, 2, 3; intermediate-risk group: score 4, 5; high-risk group: score ≥6.

LD, longest diameter; PM, parametrium.

RM, resection margin
DOI, depth of invasion

(*Int J Gynecol Cancer* 2011;21: 1646–1653)

What is the best cut of value to give adjuvant therapy?

- The best cutoff value of score 3 was confirmed by the receiver operating characteristic curve with a sensitivity of 100% and a specificity of 34.8% to 65.2%

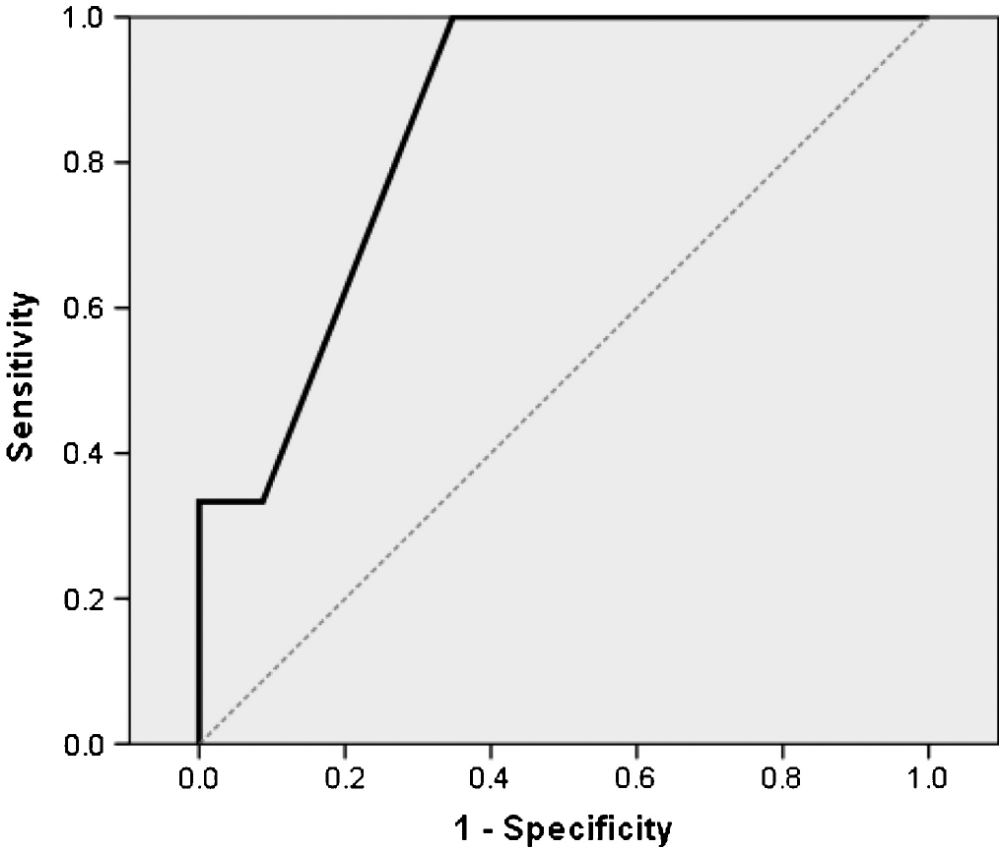


FIGURE 1. Receiver operating characteristic curve for determination of the cutoff value for risk score to identify the low-risk group, which does not need adjuvant treatment after simple hysterectomy.

(*Int J Gynecol Cancer* 2011;21: 1646–1653)

Treatment modalities

No treatment

- Surveillance

Surgery

- Radical parametrectomy, consisting of resection of the parametrium, upper vaginectomy, and therapeutic (pelvic ± paraaortic lymphadenectomy)
- Needs experienced surgeon.
- Accompanying serious bladder dysfunction has been reported in up to 10% to 32% of patients after surgey.

Radiotherapy and/or chemotherapy

- Results in a loss of ovarian function and frequent bladder, rectal, and sexual dysfunction, especially after vaginal brachytherapy.
- What type of adjuvant treatment is required?
- It is not easy to decide with simple hysterectomy findings.

Int J Gynecol Cancer 2011;21: 1646-1653
Int J Gynecol Cancer 2012;22: 1383-1388

Adjuvant therapy to whom?

- Adjuvant treatment can be omitted in low-risk group patients with invasive cervical cancer detected after SH.

- There can be one exception in this prognostic scoring system. Further treatment might be recommended to the patient, if any, who was in a low-risk group because of the one high-risk factor, that is, positive RM or LN or para-metrium (score = 3).

(*Int J Gynecol Cancer* 2011;21: 1646–1653)

Standard treatment modalities for known cervical cancer (No fertility desire)

IA1	Extrafascial or simple hysterectomy
IA2-IIA	Radical hysterectomy or radiotherapy
Bulky tumors in more than Stage IB or advanced disease such as node positive and more than Stage IIB	Concurrent chemoradiotherapy

Primary treatment

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INCIDENTAL FINDING OF INVASIVE CANCER AT SIMPLE HYSTERECTOMY

PRIMARY TREATMENT

Stage IA1 → Pathologic review → No LVSI → See Surveillance (CERV-10)

Stage IA1 with LVSI or ≥ Stage IA2 →
- H&P
- CBC (including platelets)
- LFT/renal function studies
- Imaging (optional for ≤ stage IB1):
  - Chest x-ray
  - CT or PET-CT scan
  - MRI as indicated

→ Negative margins; negative imaging → Pelvic RT[f] + brachytherapy[f] ± concurrent cisplatin-containing chemotherapy[h]

→ or → Complete parametrectomy + upper vaginectomy + pelvic lymph node dissection ± para-aortic lymph node sampling

- Negative nodes → Observe or Optional pelvic RT[f] ± vaginal brachytherapy[f] if large primary tumor, deep stromal invasion and/or LVSI
- Positive nodes and/or Positive surgical margin and/or Positive parametrium → Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy[h] ± individualized brachytherapy[f] (if positive vaginal margin)

→ Positive margins,[l] gross residual disease, or positive imaging

- Imaging negative for nodal disease → Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy[h] ± individualized brachytherapy[f] (if positive vaginal margin)
- Imaging positive for nodal disease → Consider surgical debulking of grossly enlarged nodes → Pelvic RT[f] (para-aortic lymph node RT if para-aortic lymph node positive) + concurrent cisplatin-containing chemotherapy[h] ± individualized brachytherapy[f] (if positive vaginal margin)

Surveillance

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SURVEILLANCE[m]

- Interval H&P
  every 3-6 mo for 2 y,
  every 6-12 mo for 3-5 y,
  then annually based on patient's risk of disease recurrence
- Cervical/vaginal cytology annually[n] as indicated for the detection of lower genital tract neoplasia
- Imaging (chest radiography, CT, PET, PET/CT, MRI) as indicated based on symptoms or examination findings suspicious for recurrence[o]
- Laboratory assessment (CBC, blood urea nitrogen (BUN), creatinine) as indicated based on symptoms or examination findings suspicious for recurrence
- Recommend use of vaginal dilator after RT
- Patient education regarding symptoms

→ Persistent or recurrent disease →

WORKUP

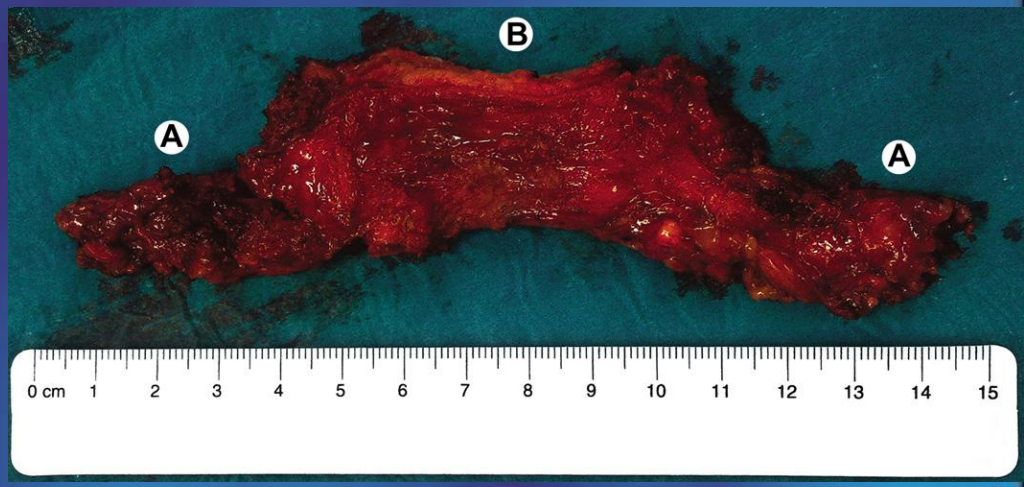
- Additional imaging as clinically indicated
- Surgical exploration in selected cases

→ See Therapy for Relapse (Local/regional recurrence) (CERV-11)

→ See Therapy for Relapse (Distant metastases) (CERV-12)

Surgery

- Resection of the parametrium, upper vaginectomy, and pelvic - paraaortic lymphadenectomy.
  - Open
  - L/S
  - Robotic



- Only lymphadenectomy
  - Open
  - L/S
  - Robotic

Parametrectomy

- Very difficult following extrafascial hysterectomy.
- Radical parametrectomy as a surgical treatment in patients with recurrent invasive cervical cancer who were initially treated with simple hysterectomy was first described by Daniel and Brunschwig in 1961.
- What is often termed parametrial tissue includes cardinal ligament, uterosacral ligament, and the tissues between (paracervical and paravaginal) lateral to the ureter which includes uterine vessels taking off from hypogastric vessels.

Cancer 1961;14:582 – 586.

Parametrectomy

- Although previous studies have indicated that all patients with positive surgical margins on simple hysterectomy specimens are poor candidates for RP, now new studies indicate that if there is no parametrial involvement, RP can be carried out safely in patients with small residual disease on the vaginal stumph.
- If there is a high probability that a patient will receive adjuvant RT or CCRT after RP, we should be carried out RT or CCRT because of the high morbidity of combination of RP and RT.

Advantages of radical parametrectomy

- Allows the assessment of the real extent of pelvic disease
- A more precise prognosis
- A proper guide for further adjuvant therapies only when needed
- Avoids radiation-related complications to the bowel, bladder and vagina.
- Most of the women would not need further treatments without detrimental effect on survival outcomes.

EJSO 38 (2012) 548e554

Studies regarding radical parametrectomy

Table 3
Literature review of studies regarding radical parametrectomy.

Author	Number of patients	Indication	Surgical approach	Site of residual disease	Intra- and post-operative complications	Further adjuvant therapies	Survival outcomes
Orr et al., 1986[14]	23	SCC: 20 Adeno: 3	ARP and PLN	Cases with residual: 6 VA +: 3 PAR +: 3 LN +: 3	Intra-operative: 7 Post-operative: 16	RT: 5	FU 35 months (median) DOD: 1
Chapman et al., 1992[15]	18	SCC: 14 Adeno: 4	ARP and PLN	Cases with residual: 2 PAR +: 1 LN +: 1	Intra-operative: 1	RT: 3	DFS 89% (5 years) Recurrence: 2 DOD: 1
Kinney et al., 1992[16]	27	SCC: 18 Adeno: 9	ARP and PLN	Case with residual: 4 VA +: 1 PAR +: 1 LN +: 2	Blood transf.: 24 Post-operative: 2	RT: 1	FU 8.4 (1.5–22.6) years Recurrence: 6 DOD: 4
Magrina et al., 1999[7]	1	EC: 1	LRP, PLN and PALN	VA +: 1 LN +: 1	None	N/A	N/A
Lee et al., 2003[8]	3	SCC: 2 EC: 1	LRP, PLN ± PALN (1)	Cases with residual: 1 VA +: 1	Intra-operative: 2	CHT: 2	N/A
Koeler et al., 2003[4]	6	SCC: 2 Adeno: 1 EC[a]: 3	LRP, PLN and PALN	Cases with residual: 4 VA +: 4	Post-operative: 1	RT: 1 CHT: 1 BRT: 2	No recurrence
Gori et al., 2004[3]	11	SCC: 8 Adeno: 3	ARP and PLN	Cases with residual: 2 PAR +: 1 LN +: 2	None	N/A	FU 75% achieve 5 years 3 (27.3%) Recurrence. 2 (18.2%) DOD
Leath et al., 2004[9]	25	SCC: 20 Adeno: 4 Small cells: 1	LRP, PLN ± PALN	Cases with residual: 4 VA +: 1 LN +: 3	Intra-operative: 2 Post-operative: 5	RT: 4 CHT: 1	FU 61 (9–103) months OS 96% (5-years) DOD: 1

Studies regarding radical parametrectomy

Liang et al., 2006[18]	6[b]	SCC: 5 Sarcoma: 1	ARP, PLN and PALN	Cases with residual: None	None	None	FU range 6–19 months No recurrence
Ayhan et al., 2006[2]	27	SCC: 19 Adeno: 5 EC: 2 Anaplastic: 1	ARP, PLN and PALN	Cases with residual: 10 VA +: 6 PAR +: 2 LN +: 6	Intra-operative: 5	11 (40.8%) RT or CCR	OS 88.89% DFS 88.67% Recurrence: 2 DOD: 1
Nezhat et al., 2007[6]	1	EC: 1	LRP, PLN and PALN	VA +: 1 (negative margins)	None	None	FU 12 months No recurrence
Ramirez et al., 2008[5]	5	SCC: 5	RRP and PLN	None	Intra-operative: 2 Post-operative: 1	None	FU 7.5 (1.3–13.8) months No recurrence
Buda et al., 2009[11]	12	SCC: 8 Adeno: 4	LRP and PLN	Cases with residual: 3 VA +: 2 LN +: 2	Post-operative: 2	CCR: 2 BRT: 1	FU 50 (13–60) months No recurrence
Park et al., 2011[17]	29	SCC: 16 Adeno: 13	ARP,[c] PLN ± PALN	Cases with residual: 7 VA +: 3 LN +: 4	Intra-operative: 3 Post-operative: 2	RT: 1 CHT: 2 CCR: 2	FU 73 (3–220)months No recurrence
Present series	11	SCC: 5 Adeno: 2 EC: 4	RRP and PLN	Cases with residual: 6 VA +: 5 PAR +: 2	Intra-operative: 1 Post-operative: 1	RT: 1 CHT: 1 CCR: 1	FU 19 (8–36) months Recurrence: 1

Data are expressed as absolute number (%), median (range) or mean ± sd SCC = occult squamous cell cervical cancer; Adeno = occult adenocarcinoma of the cervical canal; EC = Recurrence of endometrial cancer ARP = Abdominal radical parametrectomy; LRP = laparoscopic radical parametrectomy; RRP = robotic radical parametrectomy; PLN = pelvic lymphadenectomy; PALN = para-aortic lymphadenectomy + = positive involvement at final histological examination; LN = Lymph-nodes; PAR = parametrium; VA = vaginal apex. N/A = not assessed; OS = overall survival; DFS = disease-free survival; RT = radiotherapy; CCR = concurrent chemo-radiation; CHT = chemotherapy; BRT = Brachytherapy.

[a] 2 cases of EC with residual cervical stump for subtotal hysterectomy.

[b] 2 cases with residual cervical stump: 1 with sarcoma and 1 with SCC.

[c] 4 cases underwent laparoscopic management.

Oncological results of radical parametrectomy

Radical parametrectomy provided an excellent overall survival which largely overcomes the 90% (32-100%) at 5 years.

The outcomes by treatment modality with occult cervical cancer

Author	Year	*N*	Treatment modality	5-year OS rate (%)
Cosbie [16]	1963	86	RT	54
Barber et al. [15]	1968	115	RP	32
Green et al. [32]	1969	30	RT	30
		21	RP	61
Andras et al. [17]	1973	118	RT	89
Davy et al. [18]	1977	72	RT	77
Papavasiliou et al. [19]	1980	36	RT	89
Heller et al. [20]	1986	35	RT	67
Orr et al. [33]	1986	23	RP	NR
Kinney et al. [34]	1992	27	RP	82
Chapman et al. [35]	1992	18	RP	89
Roman et al. [21]	1993	122	RT	65
Fang et al. [22]	1993	73	RT	67
Choi et al. [23]	1997	64	RT	76
Crane et al. [24]	1999	18	RT	93
Huerta Bahena et al. [25]	2003	59	RT	59
Chen et al. [26]	2003	29	RT	82–95
Munstedt et al. [9]	2004	80	RT	83
Leath et al. [6]	2004	23	RP	96
Ayhan et al. [7]	2006	27	RP	89
Present study	2009	44	RT or CCRT	94[a]
		29	RP	100[a]

original article

Annals of Oncology 21: 994–1000, 2010
doi:10.1093/annonc/mdp426
Published online 25 October 2009

Management of occult invasive cervical cancer found after simple hysterectomy

J.-Y. Park, D.-Y. Kim, J.-H. Kim, Y.-M. Kim, Y.-T. Kim & J.-H. Nam*

- 147 patients (Korea 2009)
  - 47 patients stage IA1, they did not receive further treatment (surveillance group)
  - 99 patients stage IA2-IIA, most of them received further treatment.
    - 26 patients received no further definitive treatment (observation / CT group)
    - 44 patients received RT or CCRT (RT/ CCRT group)
    - 29 patients underwent RP (RP group)
    - Median follow up 116 months (3-235).

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- **Recurrence rates**
  - **Surveillance group : 48 patients 0%.**
    Median follow-up time 158 months (34-235)
  - **Observation/CT group : 26 patients (6 patients received CT) 34.6%.**
    Median follow-up time 104 months (7-232).
    10 year DFS and OS rates are 63%, 84%.
  - **Only Observation group : Recurrence rate 40%.**
  - **CT group : Recurrence rate 17%.**
  - **There is no differences in DFS and OS between the two groups.**

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Management of occult invasive cervical cancer found after simple hysterectomy

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- **Recurrence rates**
  - **RT/CCRT group : 44 patients (32 RT, 12 CCRT), 23 patients WPRT, 3 patients ICR, 18 patients both.**
    - **Median follow-up time 116 months (9-232)**
    - **The median number of CT cycles 4**
    - **3 patients had recurrence (6.8 %)**
    - **The 10 year DFS and OS rates 93%, 94%**
  - **RP+PLND group : 29 patients (19 patients underwent paraaortic LND).**
    - **The mean time from simple hysterectomy to RP 34 days.**
    - **Follow up time 73 months (3-220).**
    - **There is no recurrence no late complication.**
    - **The 10 year DFS and OS rates 100%.**

original article

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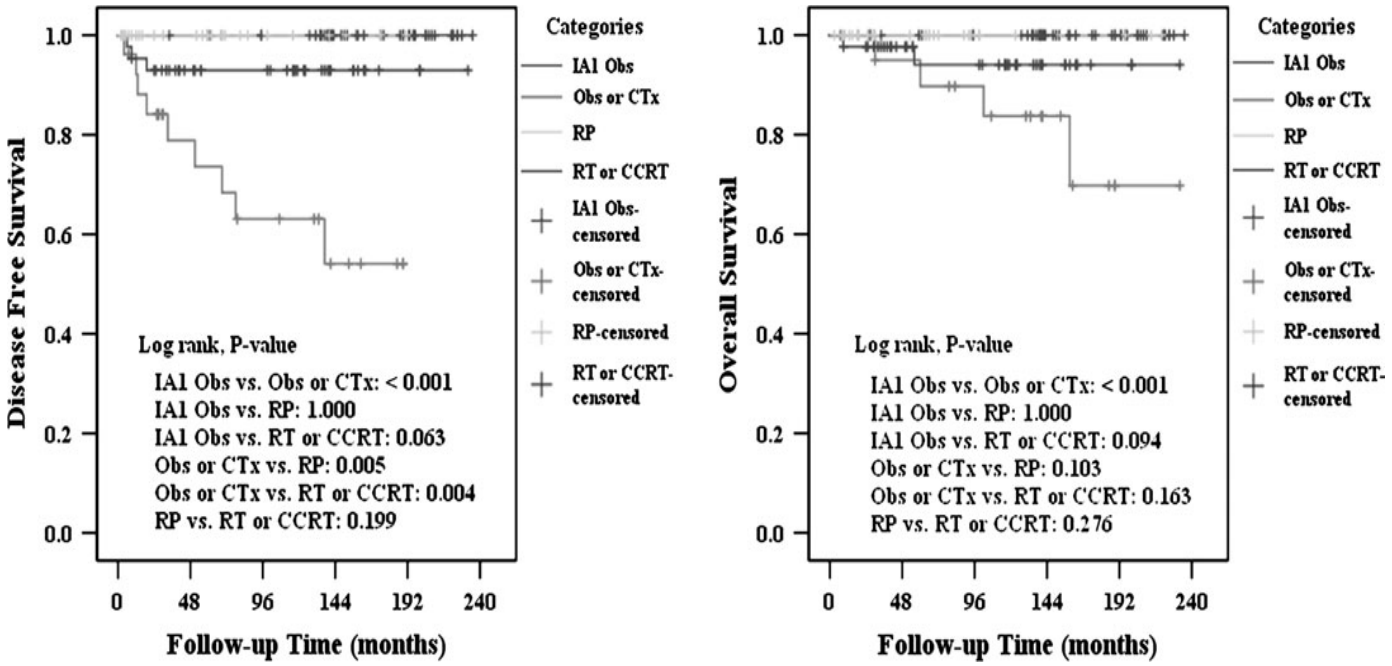


Figure 1. Disease-free survival (left) and overall survival (right) by stage and treatment modality in 147 patients with occult invasive cervical cancer. IA1 observation (Obs), 48 patients with IA1 lesions who did not receive further management; Obs/chemotherapy (CTx), 26 patients with IA2–IIA lesions who did not receive further management or who received adjuvant chemotherapy; radiation therapy (RT)/concurrent chemoradiation therapy (CCRT), 44 patients with IA2–IIA lesions who received RT or CCRT; radical parametrectomy (RP), 29 patients with IA2–IIA lesions who underwent RP.

RP and RT/CCRT

- Although RP and RT/CCRT had similar therapeutic efficacy, the lower rate of late complications observed with RP makes it preferable to RT/CCRT.
- The 5 year survival rates in cases treated with adjuvant RT are between 39-96%. However in cases treated with RP 5 year survival rates are 67-100% (FIGO IA2, IIA).
- Complication rates
  - RT/CCRT group 27 (18- 36)%
  - Open surgery 19 (8.7-30)%
  - L/S and robotic (early reports 20%, recently 7.2%)
- Complication in RT cases
  - Radiation injury to the small intestine , the rectum and the bladder.
  - In young patients ovarian and sexual disfunction.

Anticancer Res. 2013 Nov;33(11):5135-41.

Lymphadenectomy alone is a feasible option in managing incidentally-detected early-stage cervical cancer after simple hysterectomy without intermediate-risk factors: An application of the concept of less radical surgery.

Jeon HW, Suh DH, Kim K, No JH, Kim YB.

- **104 patients.**
- **An absence of IFs was associated with a longer progression-free survival than the presence of IFs in the subgroup analysis of favorable histologies.**
- **HFs could be excluded in stage IA1-IB1 cervical cancer without IFs. Omitting parametrectomy seems a feasible option for selected patients with incidentally-detected early-stage cervical cancer at simple hysterectomy, without IFs.**
- **Lymph node metastasis is the only independent risk factor for parametrial involvement.**

Laparoscopic Nerve-Sparing Radical Parametrectomy for Occult Early-Stage Invasive Cervical Cancer After Simple Hysterectomy

- 28 patients (2006-2010 Chinese)
- Median follow-up period 38 (4-62) months
- 3 patients received adjuvant therapy.
- Bladder voiding function recovery to grade 0 to grade 1was observed in 26 patients (92.9%).
- A therapeutic option for occult early-stage invasive cervical cancer discovered after hysterectomy.
- Nerve-sparing radical surgery in indicated patients may lead to optimal preservation of bladder function.

Int J Gynecol Cancer 2012;22: 1383-1388

JJCO Japanese Journal of Clinical Oncology

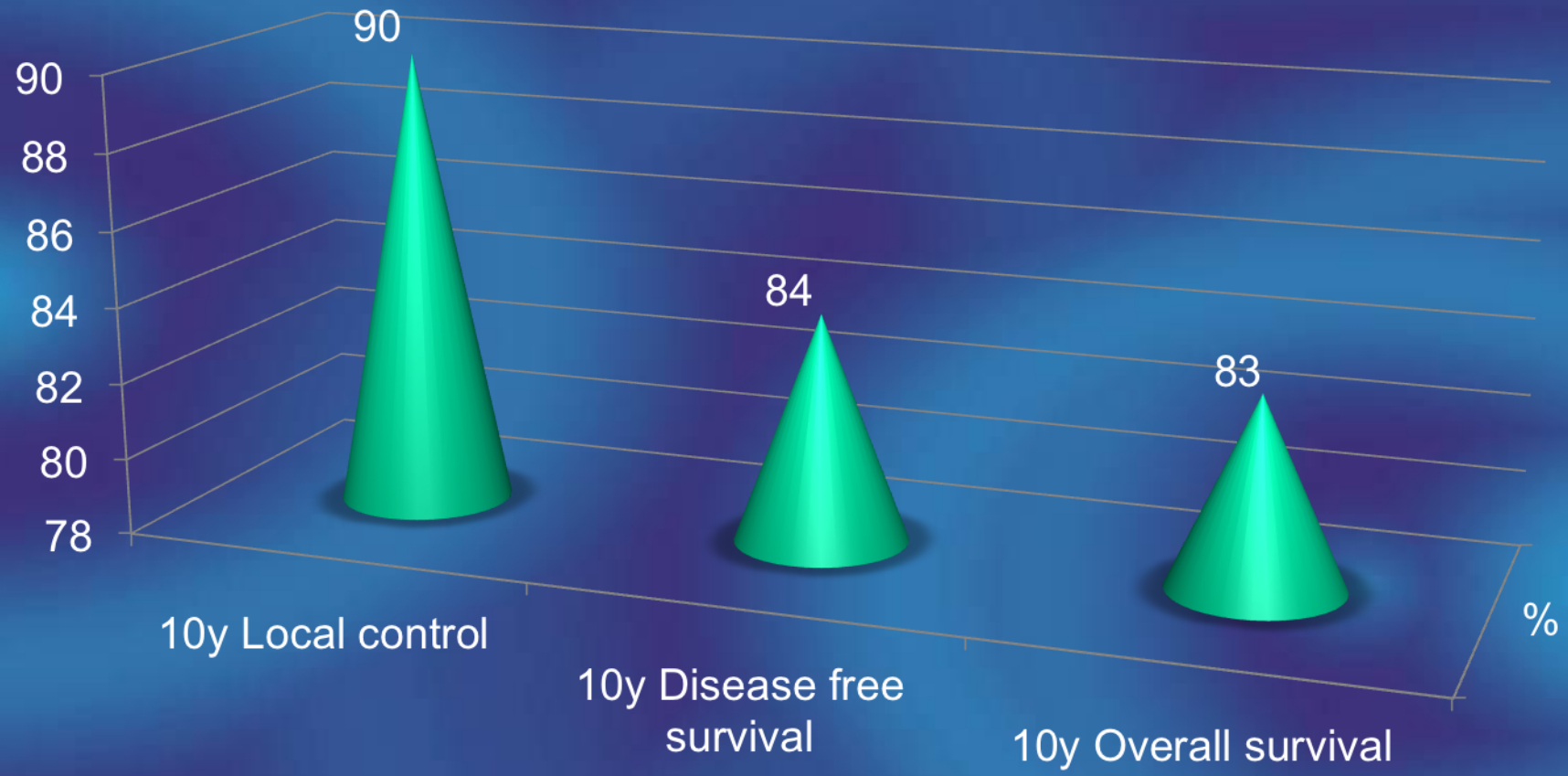
Jpn J Clin Oncol 2013;43(12)1226–1232
doi:10.1093/jjco/hyt137
Advance Access Publication 12 September 2013

Outcome Analysis of Salvage Radiotherapy for Occult Cervical Cancer Found After Simple Hysterectomy

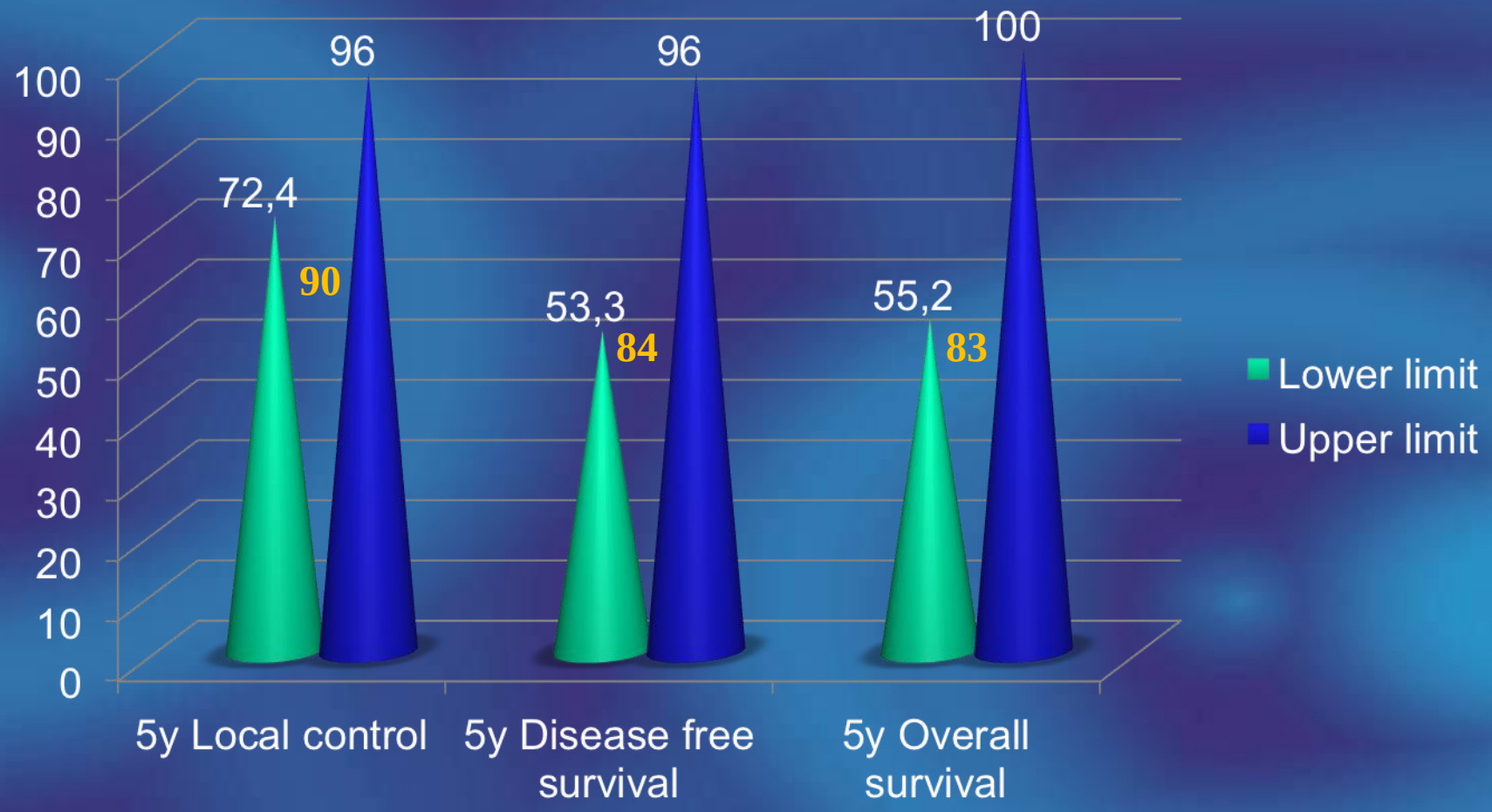
Hyeon Kang Koh[1], Wan Jeon[1], Hak Jae Kim[1,2,*], Hong-Gyun Wu[1,2,3], Kyubo Kim[1], Eui Kyu Chie[1,2] and Sung W. Ha[1,2,3]

117 patients (Korea), Stage IA, IB (mostly), median follow-up time 75 months
IIA, IIB, IIIB
EBRT /+/- ICR

Analysis of 117 patients with salvage RT



Analysis of literature findings with salvage RT



Comparison of RT and Surgery revealed similar results

	Year	Inclusion	*N*	LC (%)			DFS (%)	OS (%)				Complication
				2 years	5 years	10 years	5 years	2 years	5 years	10 years	20 years	
Radiotherapy												
Ampil et al. (6)	1987	1951–81	28	96	89	[a]		82	70			1 patient (severe)
Hopkins et al. (7)	1990	1963–87	78						68			14% (total)
Roman et al. (8)	1993	1973–87	122						65			7% (major)
Fang et al. (9)	1993	1980–88	73						67			10% (total)
Choi et al. (10)	1997	1985–93	64				77.5		75.8			
Crane et al. (11)	1999	1979–97	18		89	89			93	93		6% (major)
Chen et al. (12)	2003	1992–98	54				90		88			9.3% (G3–4 bladder)
Munstedt et al. (13)	2004	1979–98	80						83			
Hsu et al. (14)	2004	1975–94	90		85.5	80.5			85.5	74.1		1% (major)
Saibishkumar et al. (15)	2005	1996–2001	105		72.4		53.3		55.2			4.7% (major)
Smith et al. (16)	2010	1961–2004	25		96	96[b]	96		100	95	62	20% (major)
Park et al. (22)	2010	1989–2009	44				10 years:93			94		27% (total)
Present study		**1979–2010**	**117**		**92**	**90**	**87**		**87**	**83**		**5% (major)**
Operation												
Chapman et al. (17)	1992		18	LR: 3 patients					89			
Kinney et al. (18)	1992	1956–88	27						82			7% (fistula)
Gori et al. (19)	2004	1987–2003	11						75			
Leath et al. (20)	2004	1994–2000	23	LR: 1 patient					96			30% (total)
Ayhan et al. (21)	2006	1986–2004	27				88.67		88.89			18.5% (total)
Park et al. (22)	2010	1989–2009	29				100			100		17% (total)

The results of the present study is indicated as bold characters. LR, local recurrence.
[a]A blank means unavailable data.
[b]Twenty-year LC rate was also 96%.

Additional Intracaviter RT to EBRT

Additional ICR to EBRT may be omitted in patients with no residual disease and negative resection margin.

Am J Clin Oncol 2010;33: 229–232

Vaginal brachytherapy alone

- Retrospective study including 25 patients (USA, 1961-2004)
- The actuarial rate of tumor control and relapse-free survival at 5, 10, and 20 years was 96%.
- Only for patients with
  - negative postoperative imaging
  - negative surgical margins, and
  - <10 mm tumor invasion.

Am J Clin Oncol 2010;33: 229–232

Conclusion- I

- When invasive cervical cancer is found after simple hysterectomy, further treatment is mostly necessary, except very rare conditions.
- In occult cervical cancer treatment modalities are surveillance, RP and RT.
- In low risk groups (risk score <3), surveillance should be performed.
- Salvage radiotherapy (RT, CCRT, vaginal brachterapy) or radical parametrectomy should be performed in many cases (intermediate or high risk groups >3).

Conclusion- II

- If a lesion is found to be IA1 cervical cancer, further management is not required, regardless of the status of LVSI. However if the lesion in larger, definitive RT, CCRT or RP is required because higher recurrence, death rates have been observed in patients who did not receive further management or who received adjuvant therapy.
- Both treatment modalities (RP, RT) have similar oncologic outcomes but RP is feasible in all patients. Because the rate of perioperative complications is very low, and there is no late morbidity.

Conclusion- III

- Due to the high rates of long term morbidity after RT or CCRT; RP may be preferable for selected patients with IA2 – IIA occult invasive cervical cancer.
- Also RP may be of greatest benefit in young patients who want to preserve their ovarian and sexual functions.

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