

**The 3rd International Workshop of ASGO
(Seoul, August 23-24, 2014)**

Abdominal Radical Trachelectomy for Early Stage Cervical Cancer: Where are we now ?

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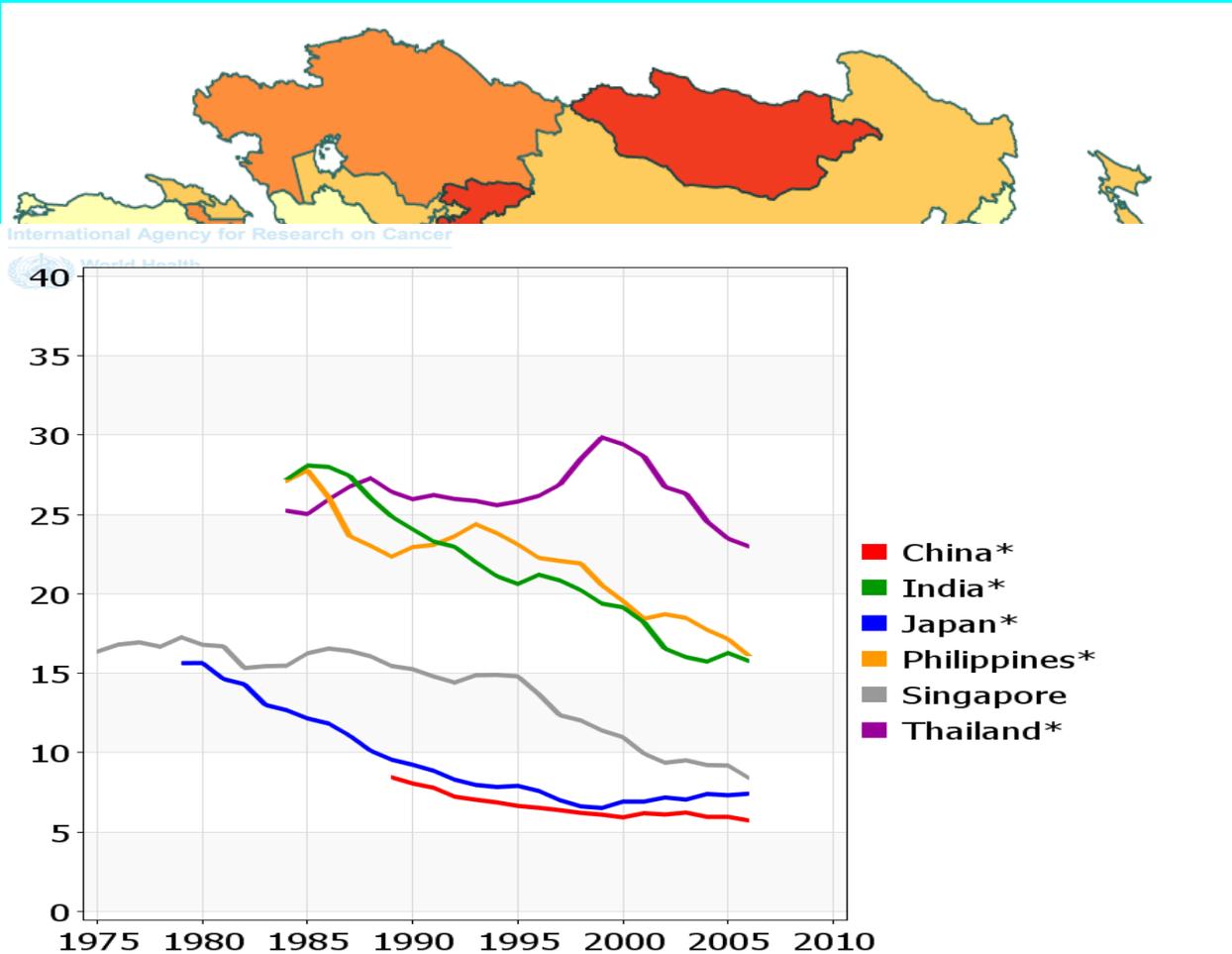
Abdominal Radical Trachelectomy for Early Stage Cervical Cancer

There is no conflict of interest to disclose
concerning this presentation

Ikuo Konishi, MD

Shinshu, Japan (Shinichi Sasaki)

Incidence of Cervical Cancer in Asia (2010)

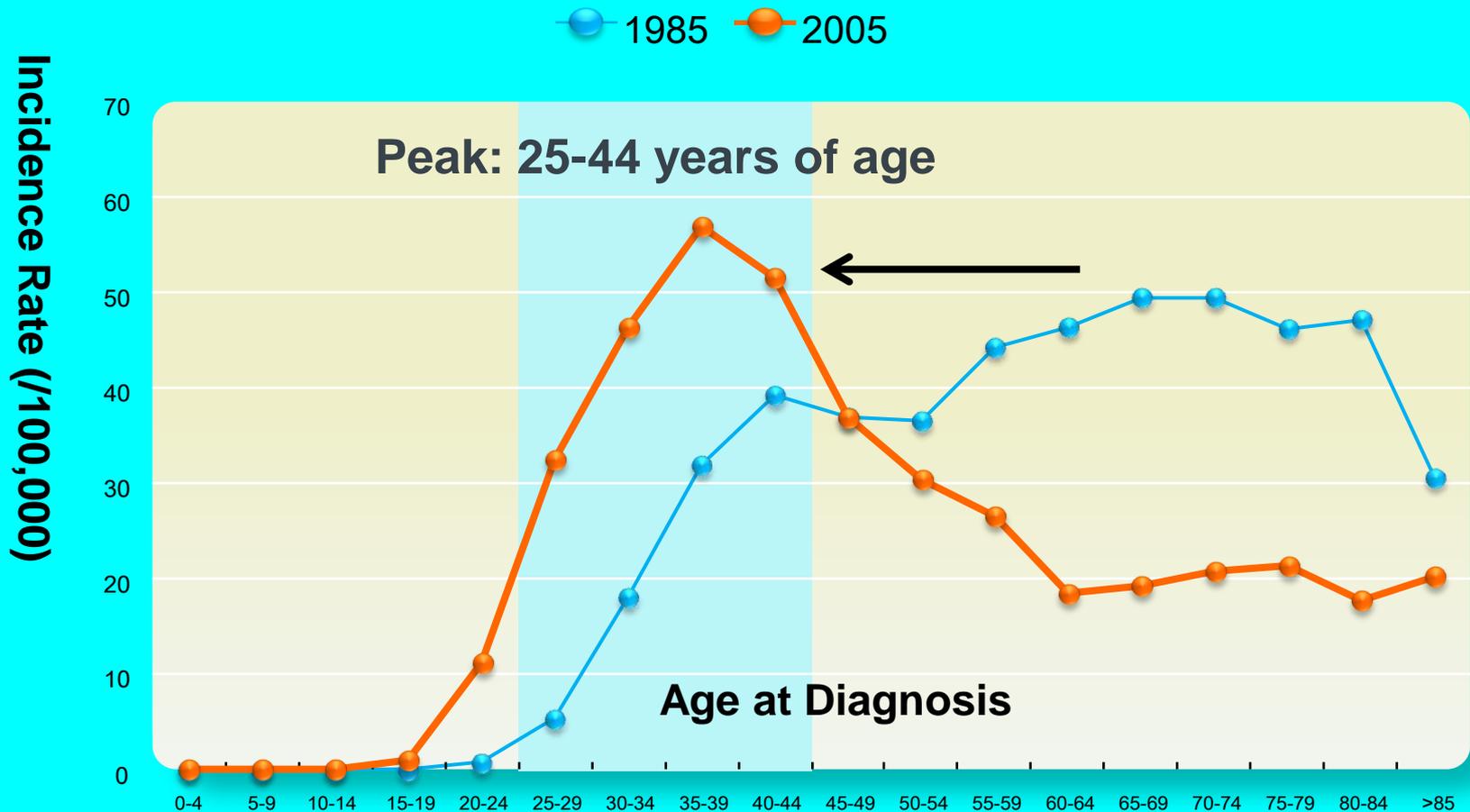


Incidence Rate (/100,000)

Nepal	32.4
Bangladesh	29.8
Mongolia	28.4
Cambodia	27.4
India	27.0
Myanmar	26.4
Thailand	24.5
Philippines	20.9
Malaysia	17.9
Indonesia	12.7
Vietnam	11.5
Korea	10.8
Japan	9.8
Singapore	6.8
Israel	5.6

Importantly, half of them are Asian women, and its decrease is still slow in Asia (WHO, 2012)

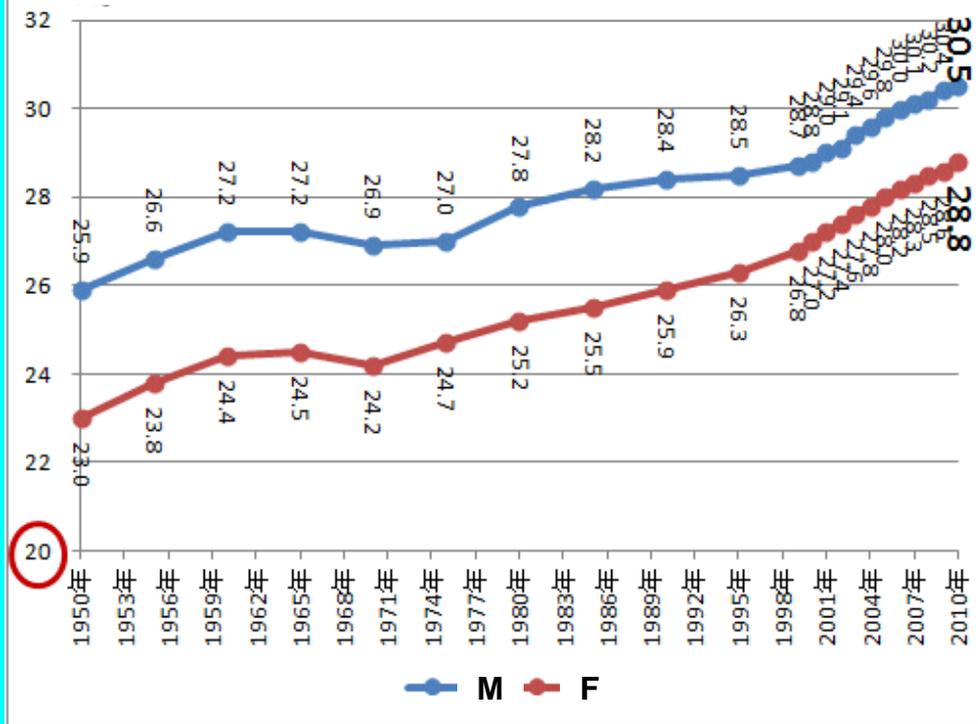
Peak of Age of Cervical Cancer has moved



In Japan, age distribution of cervical cancer has drastically been changing in the recent 20 years, and cervical cancer is now a disease of young women of 20's and 30's

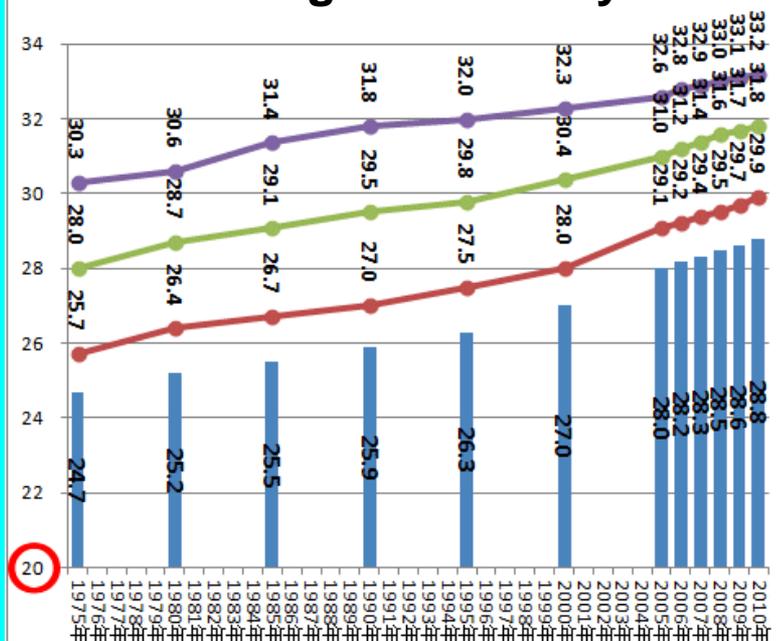
Age of Marriage and Pregnancy in Japan

Mean Age at Marriage



Mean Age of 1st Delivery
(2010) = 30.1 y

Mean Age of Delivery

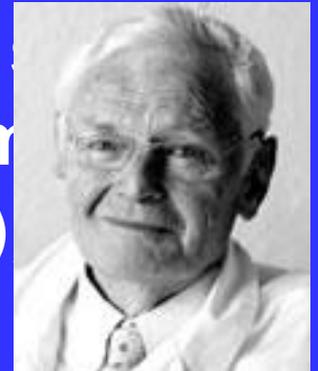


Mean Age at Marriage (2012)
Male = 30.8 y; Female = 29.2 y

Thus, young women with cervical cancer who desires fertility preservation is rapidly increasing in number !

History of Radical Trachelectomy for Early Stage Cervical Cancer

- Gyn oncologists had strongly been asked to develop radical but fertility-sparing
- In 1994, Dr. Daniel Dargent first performed vaginal radical trachelectomy (VRT) and reported its procedure in 2000
- Although VRT has been accepted in several institutions, its disadvantages are limited radicality and long learning time



Since ART has been commonly used in Japan and many other countries, I will review accumulated data on its oncology and reproductive outcomes

Abdominal Radical Trachelectomy (ART) for Early Stage Cervical Cancer

- (1) Indication and Procedure of ART
- (2) Review: oncology outcome of ART
- (3) Review: reproductive outcome of ART
- (4) Future perspective of ART

Indication of Radical Trachelectomy for Early Stage Cervical Cancer

Preoperative assessment

- Young women less than 43 years of age
- Stage IA2 and IB1; SCC or Adenocarcinoma
- Size of tumor less than 2 cm (exophytic 3 cm)
- Cancer free space below internal os in MRI
- No lymph node enlargement in CT

To achieve safety, we present the ascitic fluid, obturator and other suspicious lymph nodes, and the margin of remained cervix for pathological diagnosis → if positive, the surgery will be converted to radical hysterectomy

Oncology Outcome in Kyoto Univ Hospital

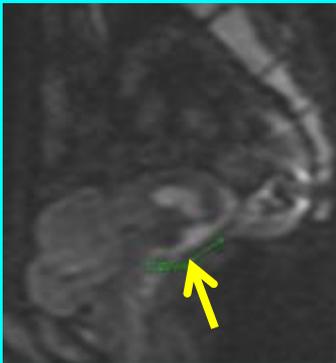
No.	Age	Status of Marriage	GP	Stage	Op time (min)	Blood loss (g)	Complication	Follow (month)	Recur
1	32	No	G2P0	IB1	300	525	Lymph cyst infection	54	-
2	38	No	G0	IB1	462	683	Lymph cyst infection	51	-
3	32	No/Yes	G0	IB1	347	290	Cervical stenosis	49	-
4	36	Divorc	G0	IB1	320	483	-	46	-
5	39	No	G0	IB1	515	820	Infection Amenorrhea	44	-
6	26	Divorc	G5P1	IB1	468	1480	-	11	-
7	35	No	G0	IB1	632	1270	Margin+→ <u>hysterectomy</u>	16	-
8	30	No	G1P0	IA2	534	750	-	31	-
9	31	Yes	G0	IB1	591	1916	Sexual dysfunction	29	-
10	33	No/Yes	G1P0	IB1	642	1320	-	27	-

Since we encountered many postoperative infections, **we abandoned the cervical drainage**. Instead, we introduced the suture (Keio Method) for endocervical extroversion, resulting in much decrease of infection

One patient was converted to radical hysterectomy due to positive margin. One patient of adenoca recurred. **Complications** were infection (3), cervical stenosis (1), amenorrhea (2), and bladder dysfunction (2)

Reproductive Outcome in our ART Series

Among 3 women who attempted to conceive, 2 became pregnant; One was abortion in the 1st trimester. And, a 32-year-old woman (No. 3 patient) was married, underwent various fertility therapies, and became pregnant after AIH, three and half years after the surgery



The pregnancy was uneventful during the 1st and 2nd trimesters, but pROM occurred at 31 weeks. A female baby 1,666g was born by Cesarean section at 32 weeks. Both mother and child are now well

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Oncology Outcome of ART: Comparison with VRT

Report of the largest series from Japan (Keio University)

- Of 71 patients, 10 were converted to hysterectomy
- Of the 61 patients of ART, 6 (10%) recurred
- Of 49 with tumor less than 2 cm, 1 (2%) recurred, vs. of 13 with tumor 2 cm or larger, 5 (38%) recurred
(Nishio et al., Gynecol Oncol 2009; 115:51-55)

Review of literature in Lancet Oncology 2011

- Of 175 patients in 6 series, fertility spared in 147 (84%). Positive lymph nodes were detected in 16%, that is higher than VRT
- Recurrence was seen in 4.8%, that is less than that of VRT. According to the size of tumor, 1.9% in tumors less than 2 cm vs. 20% in those of 2 cm or larger
(Rob et al., Lancet Oncol 2011; 12:192-200)

Oncology Outcome of ART: Comparison with VRT

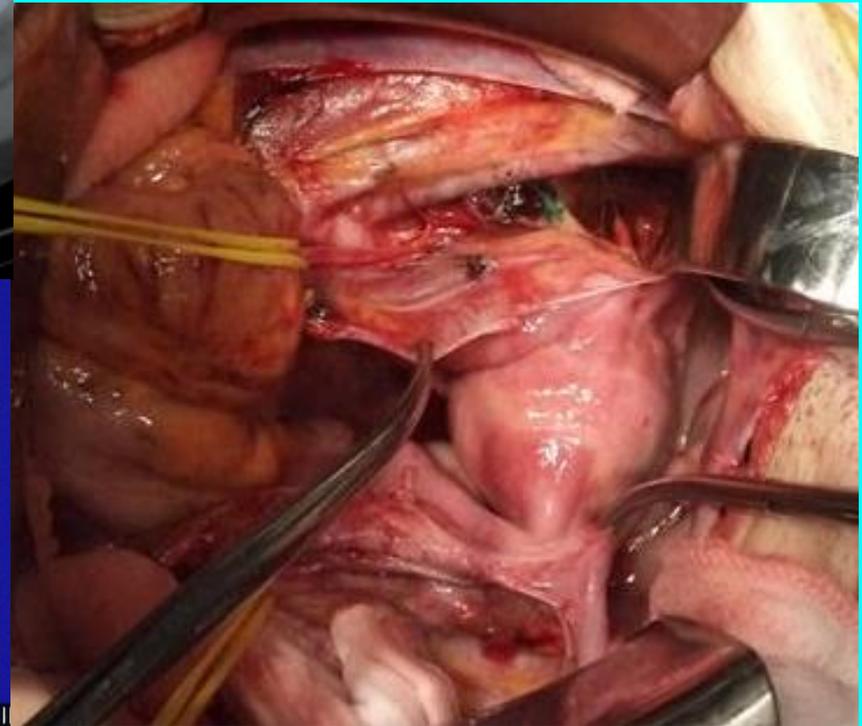
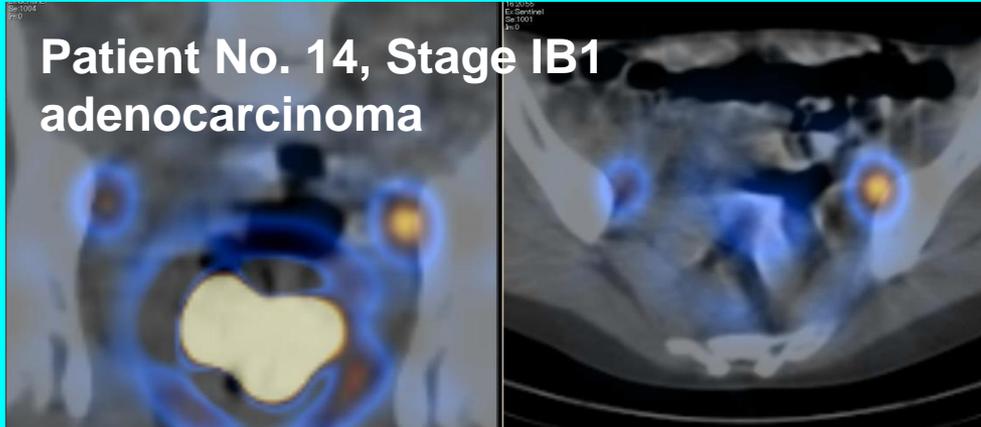
Latest review of literature in Gynecol Oncol 2013

- Of 485 patients in 44 reports, 47 (9.7%) were immediately converted to radical hysterectomy
Then, 25 received adjuv radiotherapy or hysterectomy
Finally, 413 of 485 (85%) had fertility preserved
- **Stage IB1 71%; Histology: SCC 70%, Adenoca 23%**
- **In 82% cases, size of tumor was less than 2 cm**
- Postoperative complication was seen in 35%: cervical

In summary:

- (1) Out of the patients elected as candidate for ART, fertility will be spared in 85%; Rate of overall recurrence is 4%**
- (2) Prognosis of patients with tumor less than 2 cm in size is excellent, if lymph node metastasis is excluded**
- (3) Patients with tumor of 2 cm or larger in size have higher risk of recurrence, and other strategies are needed**

To exclude Lymph Node Metastasis (+) cases, we introduced Detection of Sentinel Lymph Nodes



Preoperatively, local injection of ^{99m}Tc and lymph-scintigraphy identifies sentinel nodes. During surgery, both blue dye examination and gamma probe detection confirm the sentinel nodes, which will be resected and presented to pathology for frozen section and diagnosis

Possibility of Expanding Indication of ART to Cancer with Tumor of 2 cm or Larger in Size (1)

Report from MSK Cancer Center USA in 2013

- Of 29 (26%) in 110 patients with Stage IB1 cancer had a tumor 2 to 4 cm, 13 converted to hysterectomy and 1 to CCRT. Accordingly, 15 of 29 (52%) underwent ART
- Of 15 ART patients, 6 received postop CCRT, and the remaining 9 (31%) preserved fertility. One recurrence (Wethington et al., Int J Gynecol Cancer 2013, 23:1092-1098)

Report from Fudan University China in 2013

- Of 133 patients for ART, 62 (47%) had tumors >2cm
- Of 62 patients, 6 were converted to hysterectomy, and 27 adjuvant treatment; 20 chemotherapy, 7 CCRT.
- In total, 55 (89%) of 62 preserved fertility. No recurrence (Li et al., Gynecol Oncol 2013, 131:87-92)

NAC to expand Indication of ART to Cervical Cancer with Tumor of 2 cm or Larger in Size (2)

Recent report on NAC from Germany in 2014

- 20 patients with a tumor 2.1~5.0 cm, first underwent laproscopic lymphadenectomy, NAC with paclitaxel, ifosfamide, and cisplatin, then VRT. 9 of 20 showed CR. 2 needed CCRT. 1 recurred. 5 of 7 became pregnant (Lanowska et al., Int J Gynecol Cancer 2014; 24:586-593)

Report from China and Latest review in 2014

Expanding the indication of RT to Stage IB1 with a tumor of 2 cm or larger is a challenging issue. For this purpose, **NAC is receiving much attention**

Even for **Stage IB2 cancer**, so far, NAC followed by RT was applied in 12 patients. One patient became pregnant and had a baby at 28 weeks of gestation (Tsuji et al., Gynecol Oncol Case Report 2013; 4:13-15)

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Reproductive Outcome of ART: Comparison with VRT

Latest review of literature in 2013

- Fertility was preserved in 85% (413/485) of patients, that is almost similar to VRT (reported as 91%)
- In 77% cases, cerclage was performed during surgery
- 113 of the 298 patients followed attempted to conceive, and 67 of 113 (59%) became pregnant successfully
- Overall rate of pregnancy after ART was 16% (67/413), and this is almost similar (?) to rate 24% after VRT
- Of 67 pregnancies, abortion was seen in 18 (24%)
5 in the 1st trimester, and 9 in the 2nd trimester
Rate of abortion after VRT (30%) is almost similar
- Of 67 pregnancies, 47 deliveries were reported
12 at preterm, 19 at term, and unknown in others
- Influence of cerclage placement is controversial
(Pareja et al., Gynecol Oncol 2013; 131:77-82)

Reproductive Outcome of ART: Comparison with VRT

Report of the largest series in 2013 (Keio University)

- 114 patients underwent ART from 2002 to 2010
- 73 (72%) had undergone conization for diagnosis
- Median age was 33 years (25-40 years)
- 11 (12%) received adjuvant chemo- or radio-therapy
- Out of 69 patients who attempted to conceive, 25 (36%) became pregnant; a total of 31 pregnancies
- Among 31 pregnancies, 9 (29%) by natural conception, 2 (6%) by AIH, and the remaining 20 (65%) by IVF-ET

In summary:

(1) Pregnancy rate after ART may be comparable to that after VRT. However, **rate of natural conception seems to be lower**, and assisted reproductive technologies are needed for conception after ART

(2) **pROM and preterm delivery**, sometimes before 29 weeks, is frequent in both VRT and ART

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ART for Cervical Cancer: Where are we now?

- (1) Abdominal radical trachelectomy (ART) is feasible for Stage IB1 cervical cancer in young woman desiring fertility preservation
 - (2) Fertility-sparing is possible in 85% patients elected as candidate for ART
 - (3) Oncology outcome is excellent, if the tumor is less than 2 cm and having no risk factors
 - (4) Although many patients need various fertility therapies for conception, final reproductive outcome is comparable to VRT
- # Therefore, ART is one of standards for fertility-sparing surgery for Stage IB1 cervical cancer**

ART for Cervical Cancer: Future perspective

- (1) For the tumor of 2 cm or larger, introduction of neoadjuvant chemotherapy (NAC) is an important issue to be challenged**
- (2) For better reproductive outcome, further improvements on surgical techniques and on perioperative/ perinatal care is mandatory**
- (3) Recently, promising results of LRT has been reported from Korea, Japan, China, and UK**
 - (Lu et al., Gynecol Oncol 2013; 130:275-279)**
 - (Ebisawa et al., Gynecol Oncol 2013; 131:83-86)**
 - (Park et al., J Gynecol Oncol 2014; 25:9-13)**
 - (Park et al., J Surg Oncol 2014; 110:252-257)**
 - (Kucukmetin et al., Int J Gyn Cancer 2014; 24:135-9)**

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- (5) Appendix:
Cervical cancer in early pregnancy

Cervical Cancer in Early Pregnancy: Another Serious Issue

Guideline on Cervical Cancer during Pregnancy

- Cancer of Stages II or more should be treated immediately by surgery or radiotherapy
- Treatment of Stage IB small tumor in the 2nd trimester can be postponed until the 3rd trimester for a few months since such

In clinical practice, however, maintenance of the current pregnancy is strongly desired by patient and her partner. Thus, another strategies for management of Stage IB cervical cancer in early pregnancy should be considered

Cervical Cancer in Early Pregnancy: The 2 answers are proposed

One: Radical Trachelectomy during Pregnancy

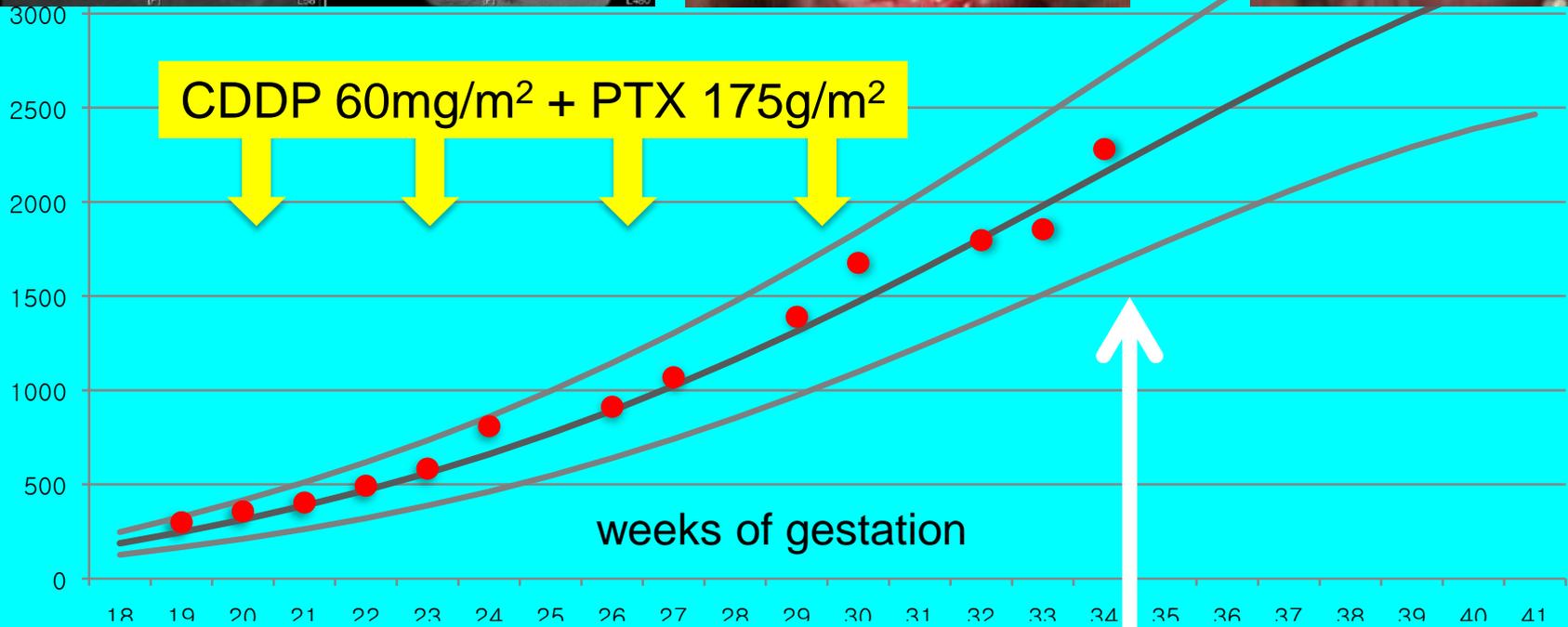
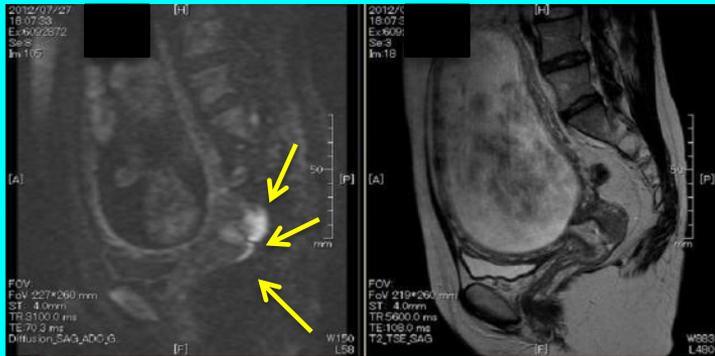
- For Stage IB1 cancer, size of tumor <2 cm, more than 14 patients underwent ART or VRT
However, fetal loss rate is very high (5 of 14)
(Morice et al., Lancet Oncol 2012; 379:558-69)

Another: Neoadjuvant Chemotherapy (NAC)

To date, safety of chemotherapy for mother and fetus has been reported from the experiences of various cancers in pregnancy (Lancet Oncol 2012).

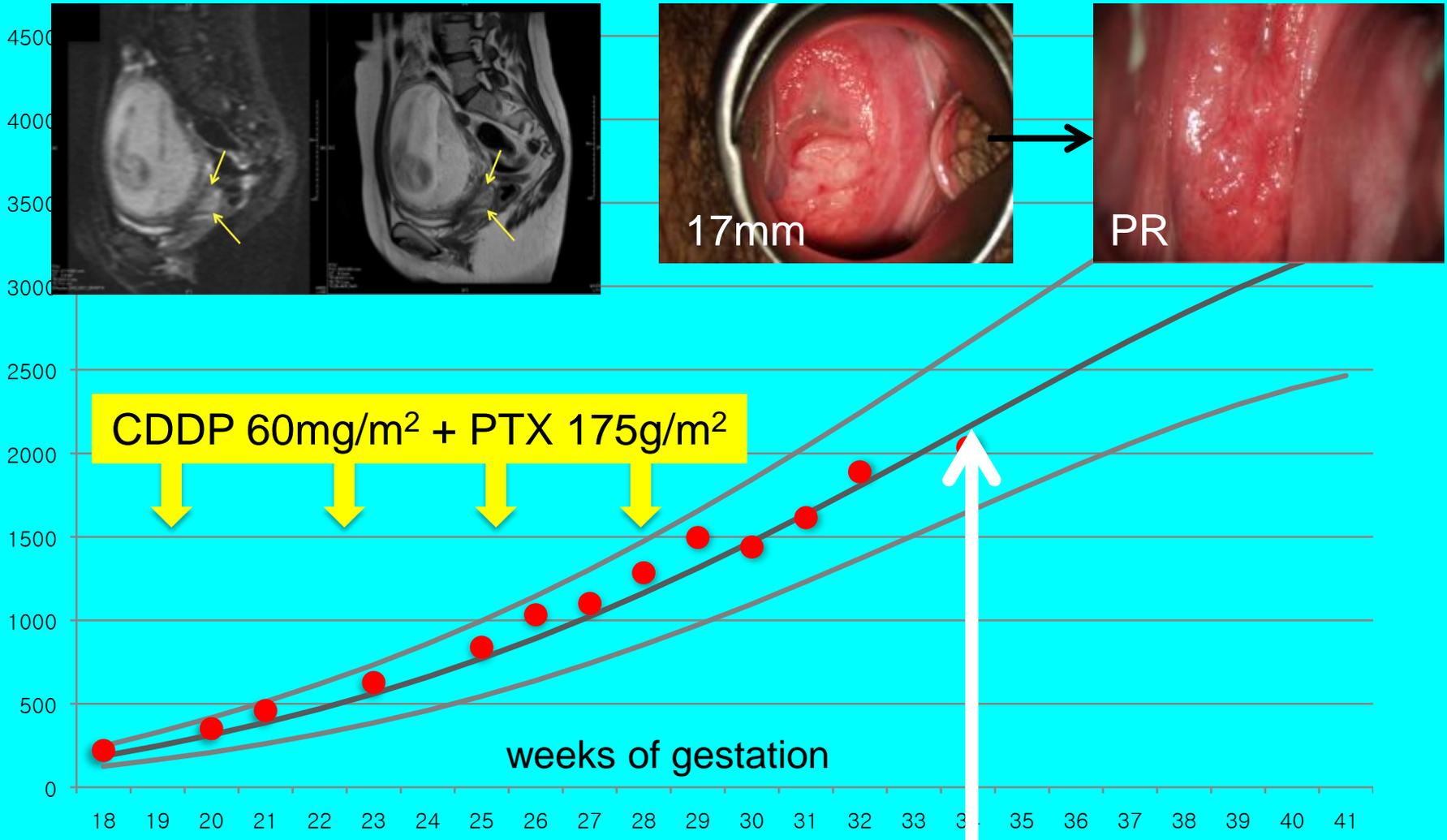
So, we have introduced NAC during pregnancy and encountered 2 patients with Stage IB1 cervical cancer

35 y.o. G2P1 Stage IB1 (SCC) Preg 16 weeks



At 34 weeks, she had Cesarean section and radical hysterectomy. Baby was 2,142g, Apgar 8/9, and had no apparent abnormalities

36 y.o. G2P0 Stage IB1 (Adenoca) 15 weeks



At 34 weeks, she had Cesarean section and radical hysterectomy. Baby was 2,016g, Apgar 8/9, and had no apparent abnormalities

Neoadjuvant Chemotherapy (NAC) in Pregnancy

In Letter to Editor, Morice et al. claimed that (1) For Stage IB1, another strategy, either expectant management after lymphadenectomy or radical trachelectomy in pregnancy, might also be considered

(2) For Stage IB2, oncology outcome in this series seems to be inferior to that in non-pregnant group

So, they do not agree with the conclusion of the authors

The authors described that, considering the risk factors in this series, oncology outcome of NAC group seems to be similar to non-pregnant group. Thus, NAC for locally invasive cancer during pregnancy is a reasonable option

- Of the 12 Stage IB1 patients, 11 were alive and 1 patient with small cell carcinoma recurred and died of disease
- Of the 14 Stage IB2 patients, 7 recurred and 5 died
(Fruscio et al., Gynecol Oncol 2012; 126:192-197)

Cervical Cancer in Early Pregnancy: Current Status of NAC

- **Safety of chemotherapy during pregnancy from 2nd trimester has been almost confirmed**
- **For chemotherapy regimen, cisplatin and paclitaxel is recommended during pregnancy**
- **For Stage IB1 cancer, NAC may be a safe and reasonable option for delivery delay**
- **However, for tumors of Stage IB2 or more, oncology outcome is not yet guaranteed**
- **Therefore, NAC remains still controversial and further examination and trials are needed**



THANK YOU FOR YOUR ATTENTION !

**I sincerely thank
Prof. Joo-Hyun Nam and
for kind invitation and hospitality**

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