Recent Updates in Cervical Cancer

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Chairperson, FIGO Committee for Gynecologic Oncology (2015-18)

Secretary-General, IFCPC; Council Member, ASGO

Past President, AOGIN; Past President, AGOI

What is new in CaCx in 2018-19?

- GLOBOCAN 2018
- Revised FIGO Staging of CaCx 2018
- LACC trial and its implications
- National Program for Screening for Oral, Breast and Cervical Cancer
- HPV vaccination programs – Punjab, Sikkim, Delhi
- Updates in HPV vaccination
- WHO Call for Elimination of Cervical Cancer by 2030

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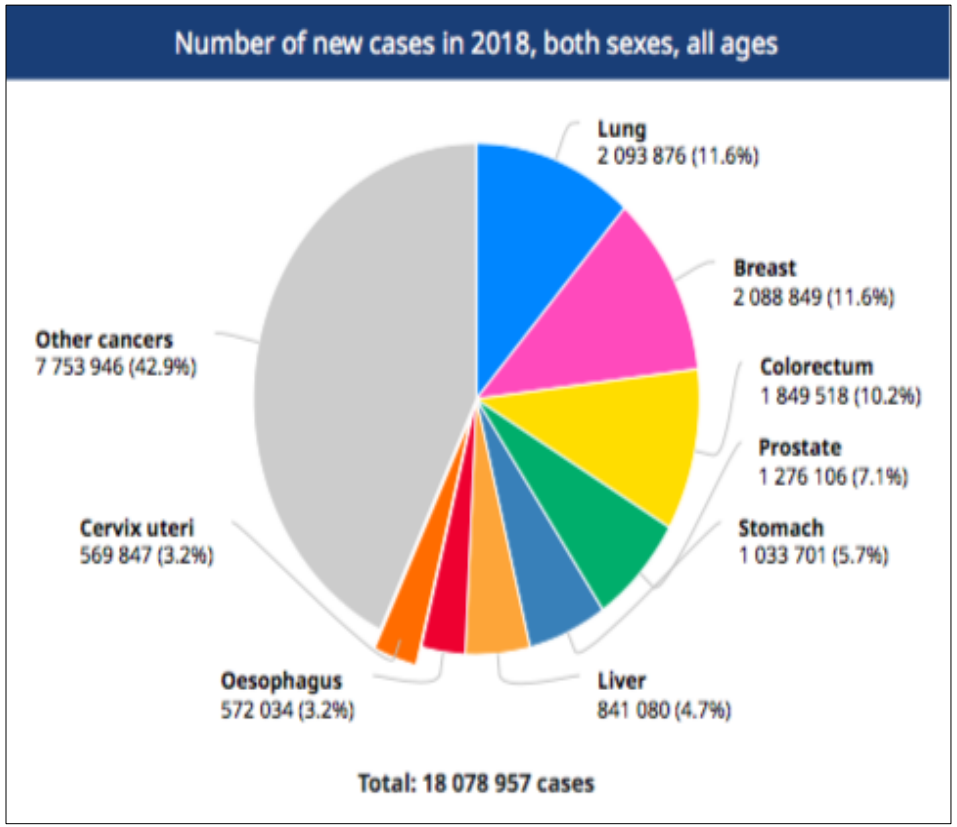
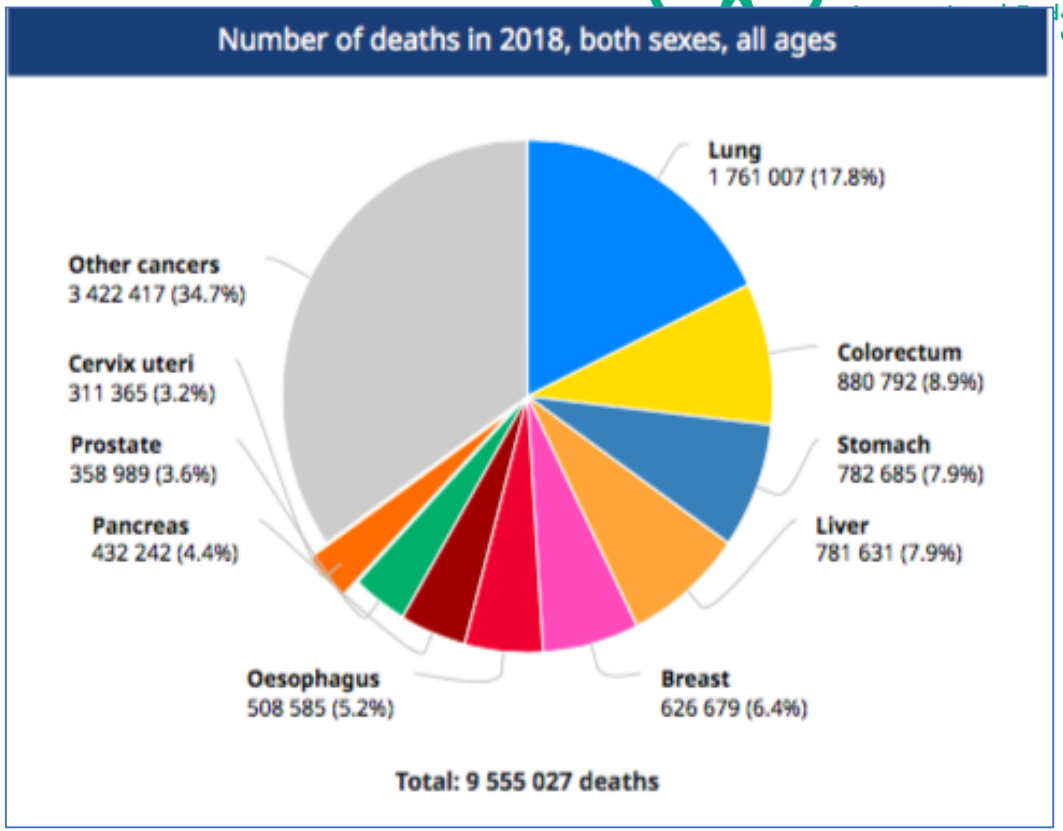
GLOBOCAN 2018

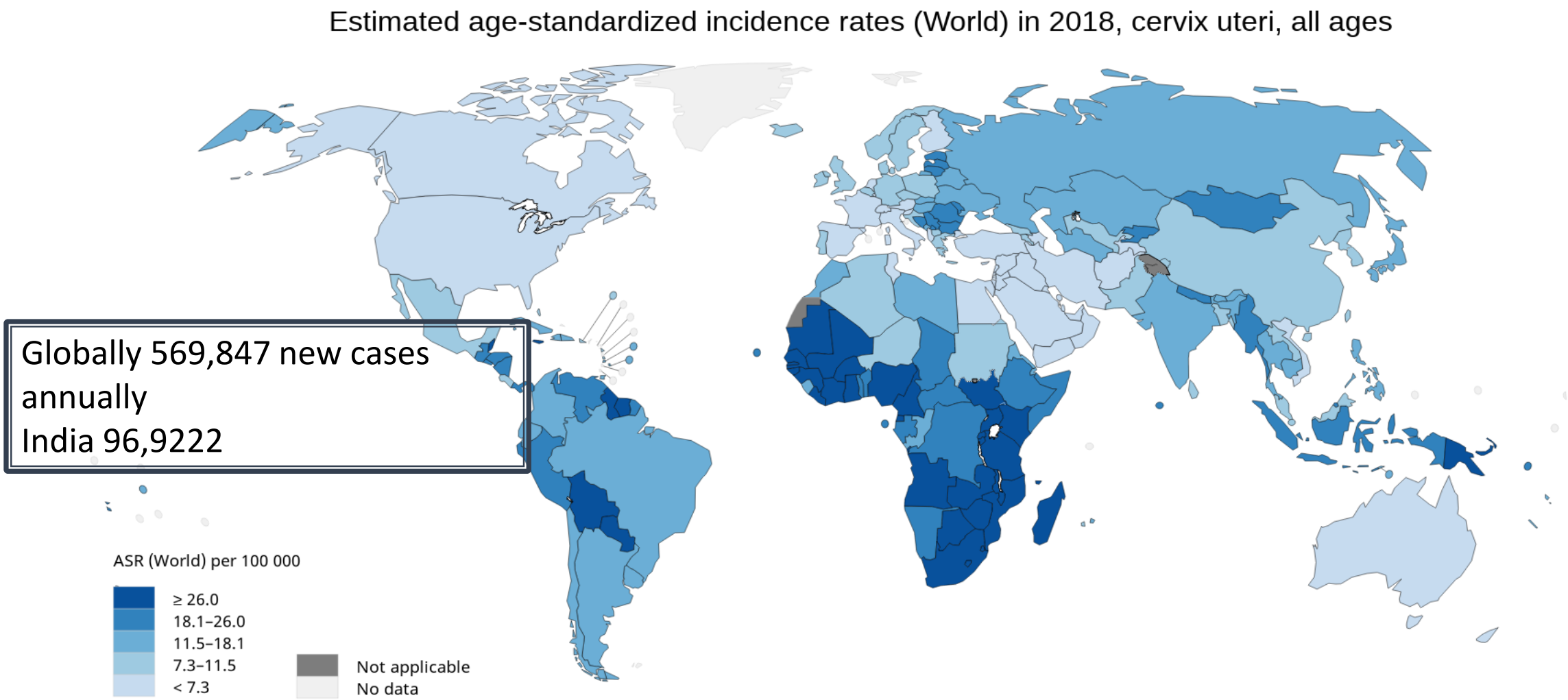




Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

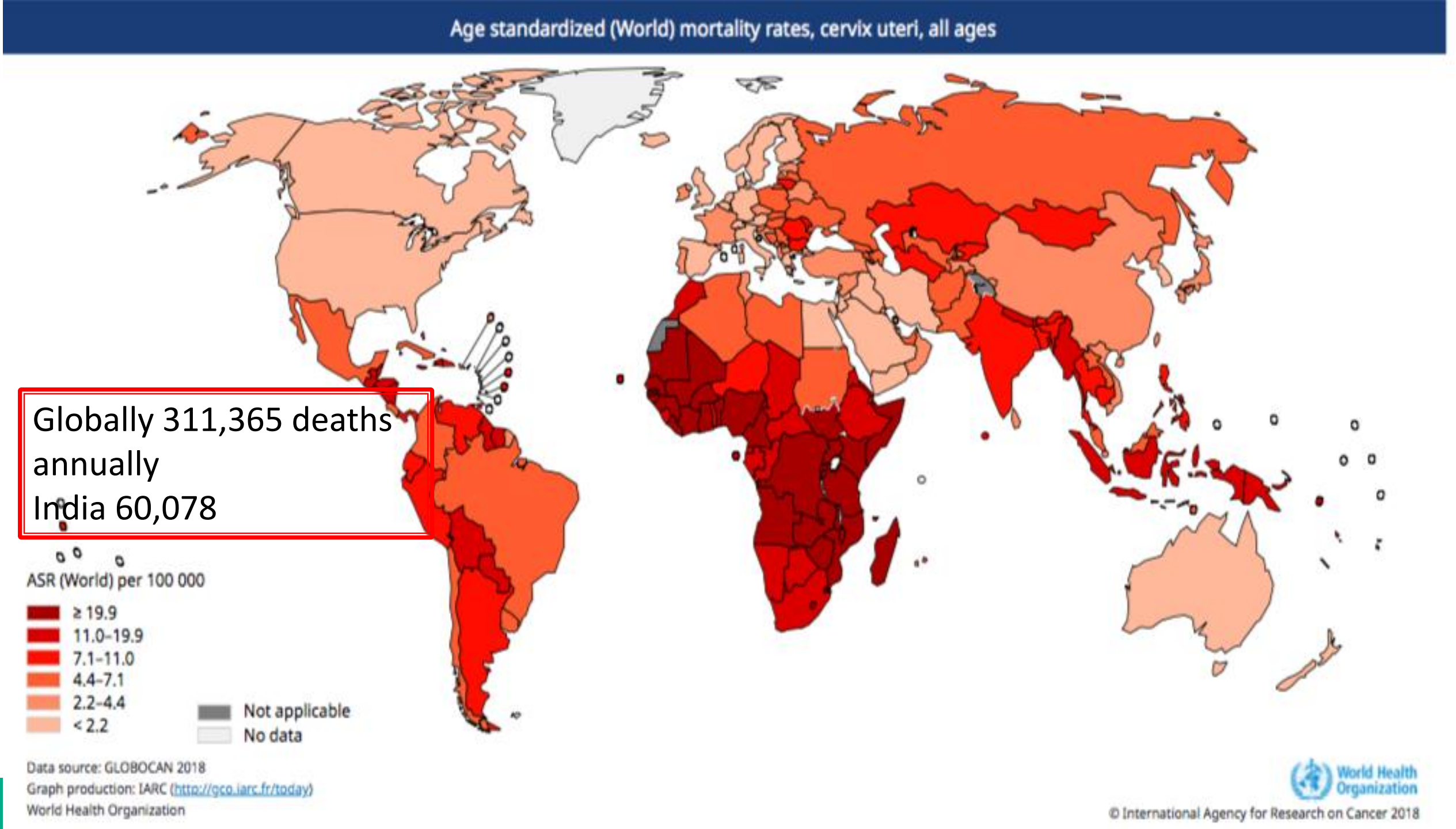
Bray F, et al. CA: Cancer j Clin. 2018;68(6):394-424.

Cervical cancer – an avoidable NCD with gross inequities (GLOBOCAN 2018)



Globally 569,847 new cases annually
India 96,9222

Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization


Age standardized (World) mortality rates, cervix uteri, all ages
Globally 311,365 deaths annually
India 60,078
ASR (World) per 100 000
≥ 19.9
11.0–19.9
7.1–11.0
4.4–7.1
2.2–4.4
< 2.2
Not applicable
No data
Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization
World Health Organization
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REVISED FIGO STAGING

Evolution of FIGO staging

1928	1929	1930	1958	2009
Radiological sub - commission of the health organization	League of Nations classification on cervical cancer	Working on providing uniform language for staging	First FIGO Staging	Last revision of FIGO Staging

Cervical cancer was the first cancer to be assigned a staging system !

FIGO's perspective on staging

- FIGO is sensitive to different resources in various parts of the world and the need for equal participation and access from less resourced countries
- In endometrial and ovarian cancers, where the mainstay of treatment is surgery, changed to surgico-pathological staging (last revision in 2009 and 2014 respectively)
- Cervical cancer, mainly a disease of low resource regions, with radiation an important treatment option, continued to be staged clinically (last revision in 2009).

Changes in scenario since 2009

- Imaging capability increased significantly globally
  - Though significantly lacking in many regions that bear the burden of cervical cancer, advanced imaging technology is available in many parts of LMICs also
  - Image-guided FNA also being practiced at several centers
- Advances in minimally invasive surgery (MIS)
  - Increased practice of “surgical staging” even without MIS.
- Increasing use of fertility-sparing surgery (radical trachelectomy)
  - Data on correlation of size of tumor with outcomes

Cervical cancer staging – Questions

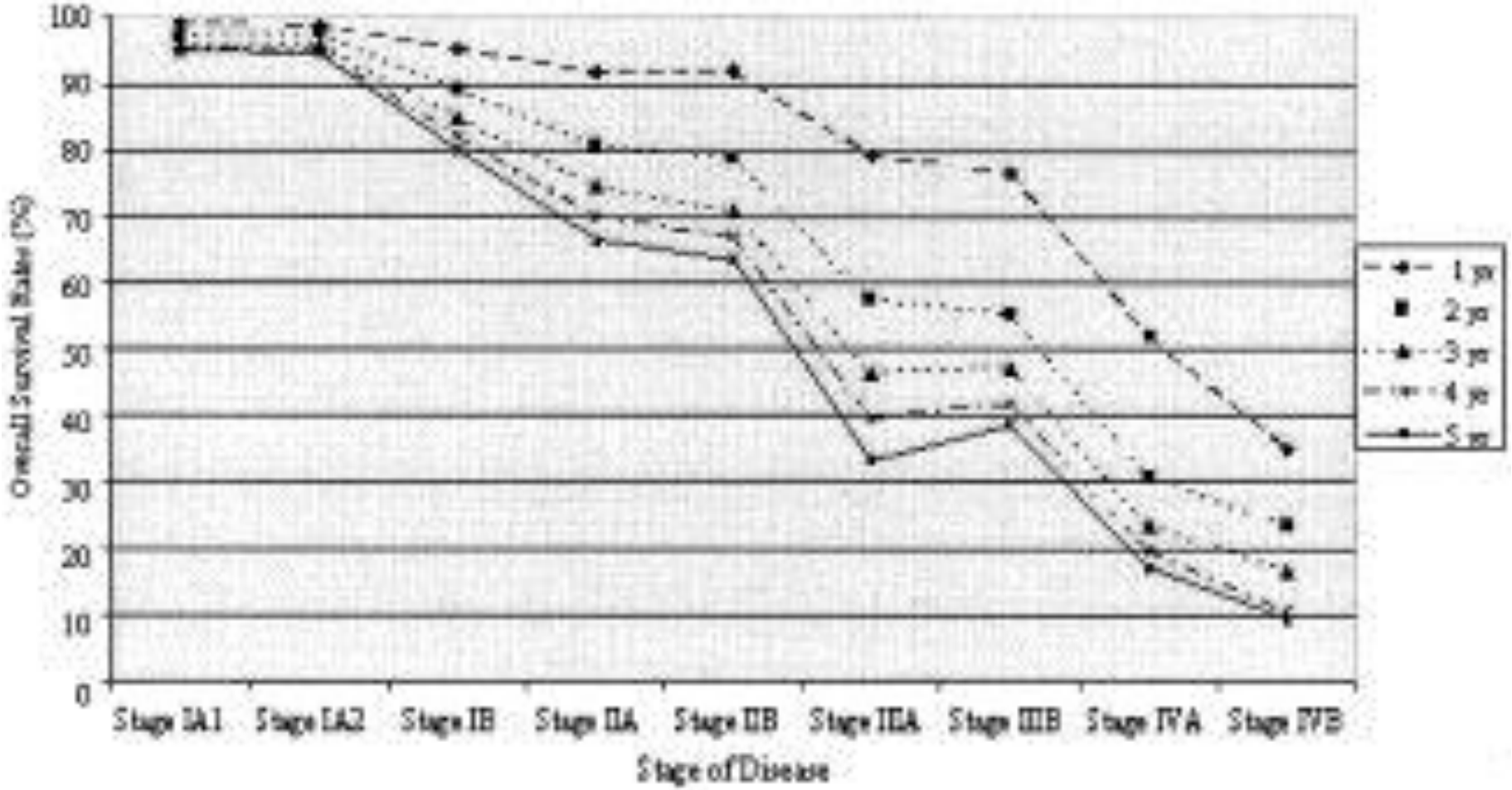
⌘ Should it continue to be clinical?

✓ Should we include lymph node status and pathological findings on tumor size in staging?

✓ Should we include imaging in staging?

✗ Should we have different staging for different resource settings?

Stage wise survival in cancer cervix



Follen M et al. Imaging in cancer. Cancer 2003;98(S9):2028-2038

Accuracy of clinical staging of CaCx

- 24%–39% error rate in staging by clinical exams[1,2,3]
- Without cross-sectional imaging, poor evaluation of deep pelvic invasion
- Accuracy in early stage[4,5]
  - IA1-IB1 85%
  - IIA 35%
  - IIB 21%

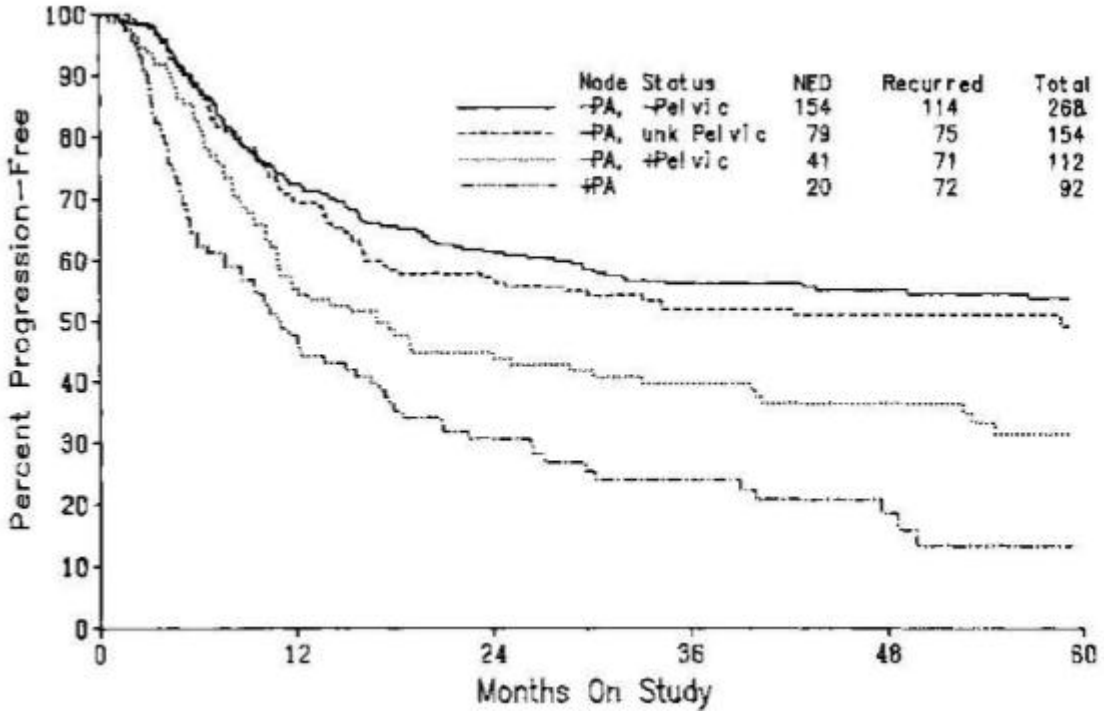
1. Narayan K et al. Relation between FIGO stage, primary tumor volume, and presence of lymph node metastases in cervical cancer patients referred for radiotherapy. Int J Gynecol Cancer 2003;13:657–663.
2. Bipat S et al. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol 2003;91(1):59–66.
3. Chuang HH et al. Can preoperative MRI accurately predict nodal and parametrial involvement. In early stage cervical cancer. Japanese J Clin Oncol 2007;37(5):370–375,
4. Pecorelli S et al. Revised FIGO staging for carcinoma of the cervix. Int J Gynecol Obstet 2009;105(2):107–8.
5. Sala E et al. The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know. Radiology 2013;266(3):717–40.

Clinical staging – Lacunae

- Significant prognostic factors are not assessed
  - Tumor volume
  - Nodal metastasis
  - Stromal invasion
  - Lower uterine segment involvement
- Data collection is incomplete for further research when based only on clinical staging

Prognostic value of nodal metastases

- Meta-analysis by Gynecologic Oncology Group (GOG)
- Studied 626 patients from GOG protocols 24, 56, and 59 with cervical carcinoma
- **Para-aortic node status and pelvic node status were significantly associated with progression-free survival**



Stehman FB et al. Carcinoma of the cervix treated with radiation therapy: I. A multivariate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer* 1991:67: 2776-2785

Prognostic value of tumor size

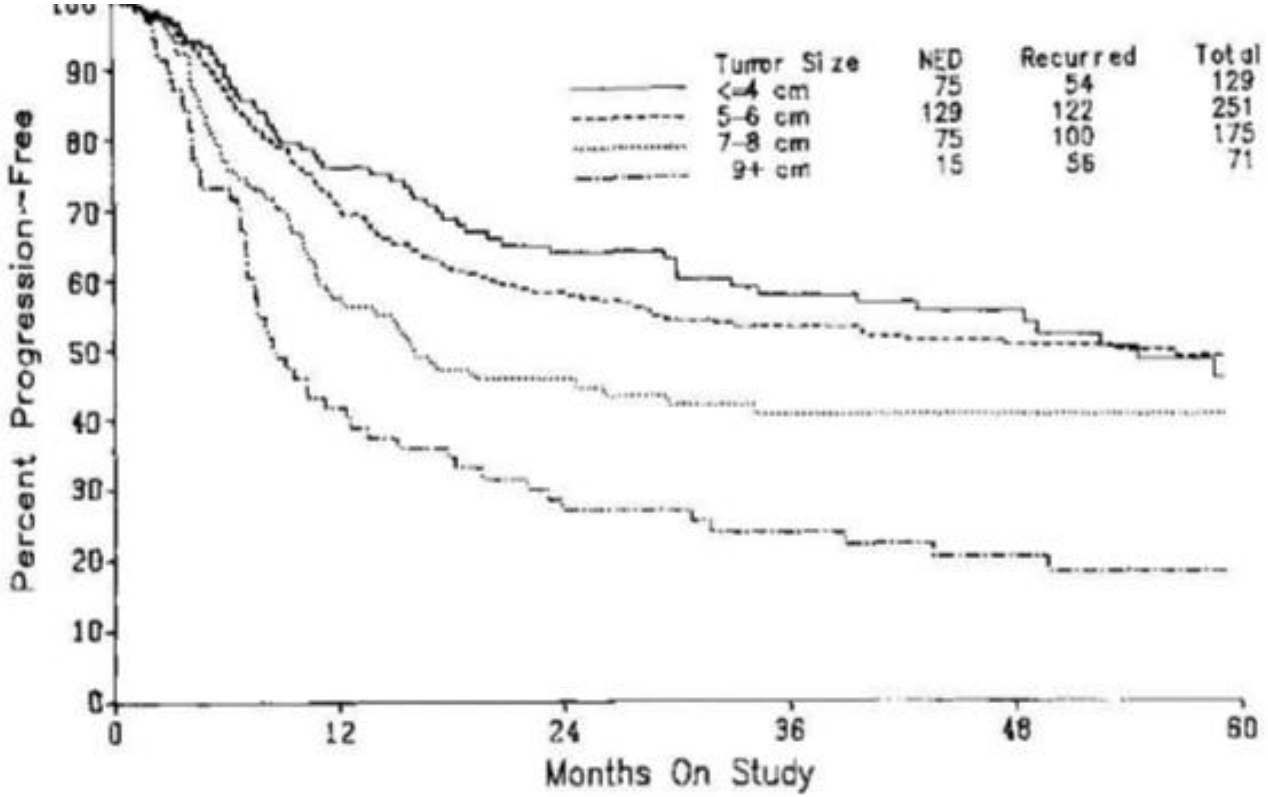


FIG. 1. Progression-free interval by tumor size.

Stehman FB et al. Carcinoma of the cervix treated with radiation therapy: I. A multivariate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer* 1991:67: 2776-2785

Risk of Parametrial Spread in Small Stage I Cervical Carcinoma

Pathology Review of 223 Cases With a Tumor Diameter of 20 mm or Less

Boris Vranes, MD, Svetlana Milenkovic, MD,† Milos Radojevic, MD,* Ivan Soldatovic, MD,‡ and Vesna Kesic, MD, PhD**

Conclusions: Risk of parametrial spread of 0.45% for tumors less than 20 mm in diameter, no LVSI, and a depth of invasion within the inner third.

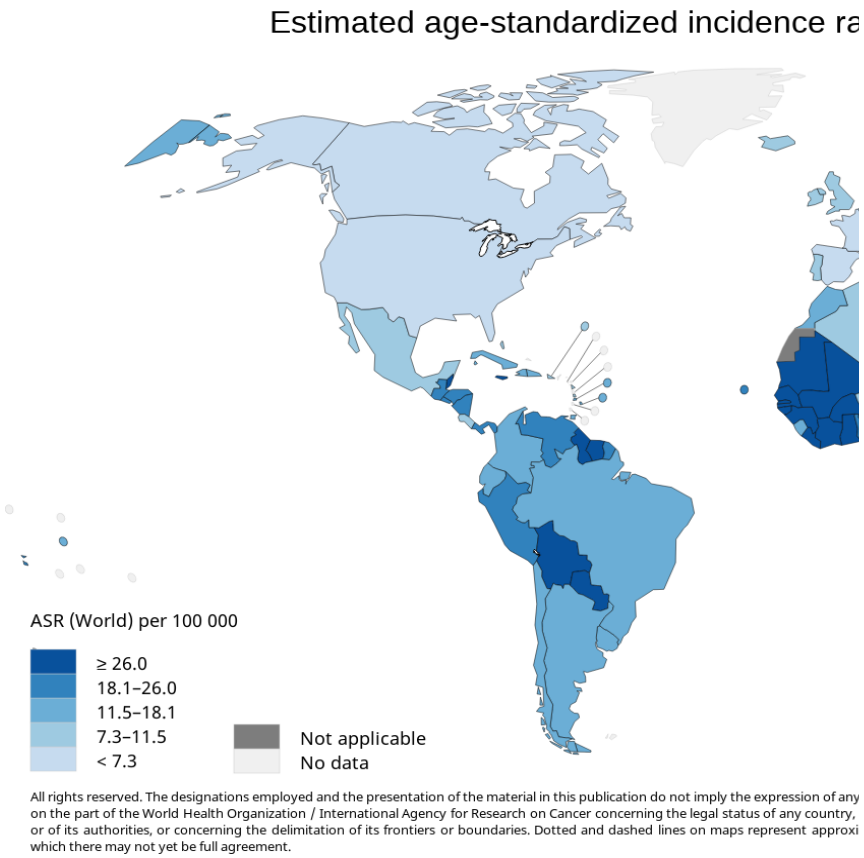
Int J Gynecol Cancer 2016 Feb;26(2):416-21 (Belgrade, Serbia)

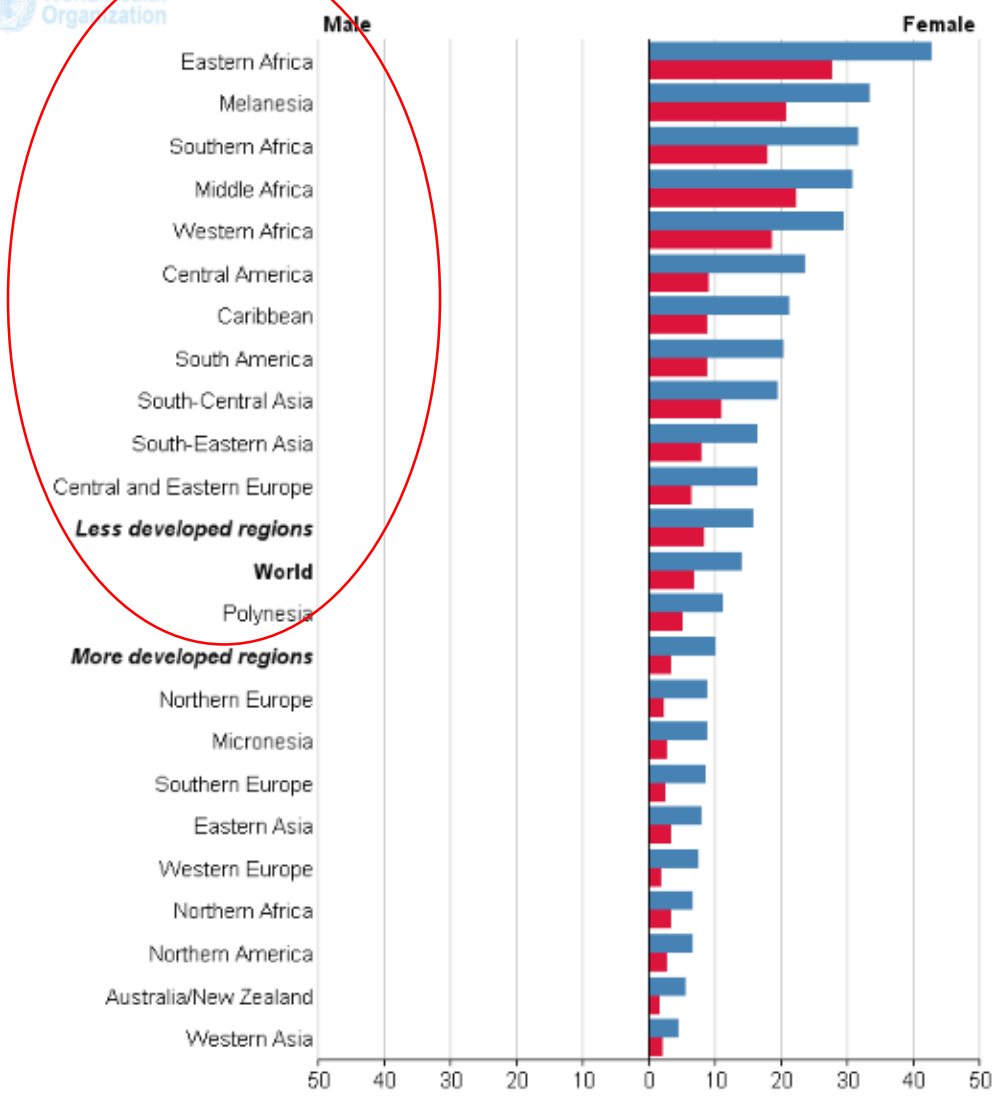
Advantages of Imaging

- Obviates the use of invasive procedures such as cystoscopy and proctoscopy, especially when there is no sign of local extension
- Identify important prognostic factors such as lesion volume and metastatic lymph nodes
  - Can upstage or downstage disease
  - Avoid multi-modality management
    - especially needed with increased screening and early detection
  - Less radiation side effects when planned without hysterectomy than as postoperative adjuvant RT

Mayr NA et al. Cervical cancer: application of MR imaging in radiation therapy. Radiology 1993; 189:601-608
Subak LL et al. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging. Obstet Gynecol 1995; 86:43-50.
Togashi K et al. Cervical cancer. J Magn Reson Imaging 1998;8:391-397.

Incidence of cancer cervix





Do we have adequate imaging facilities?

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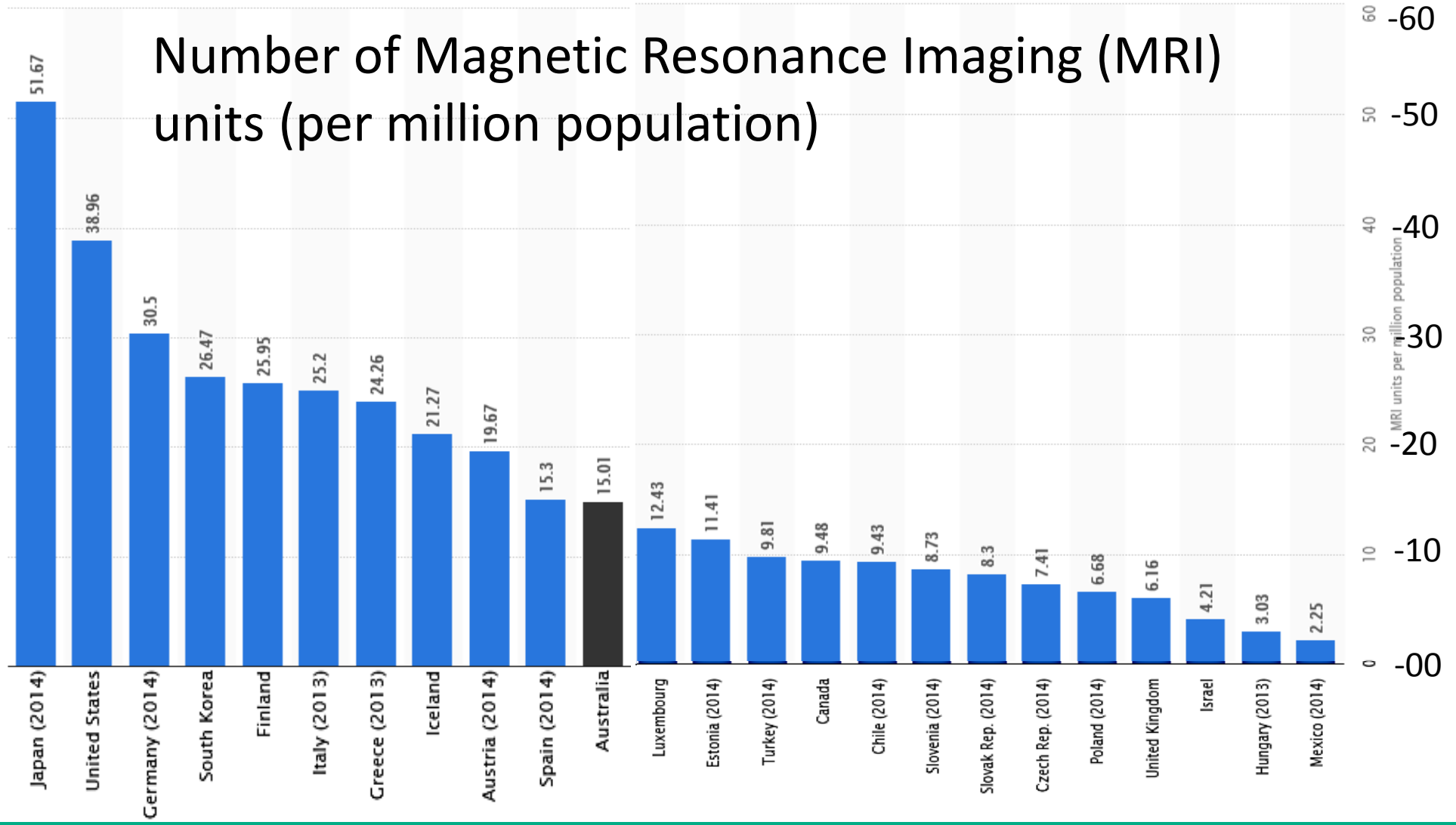
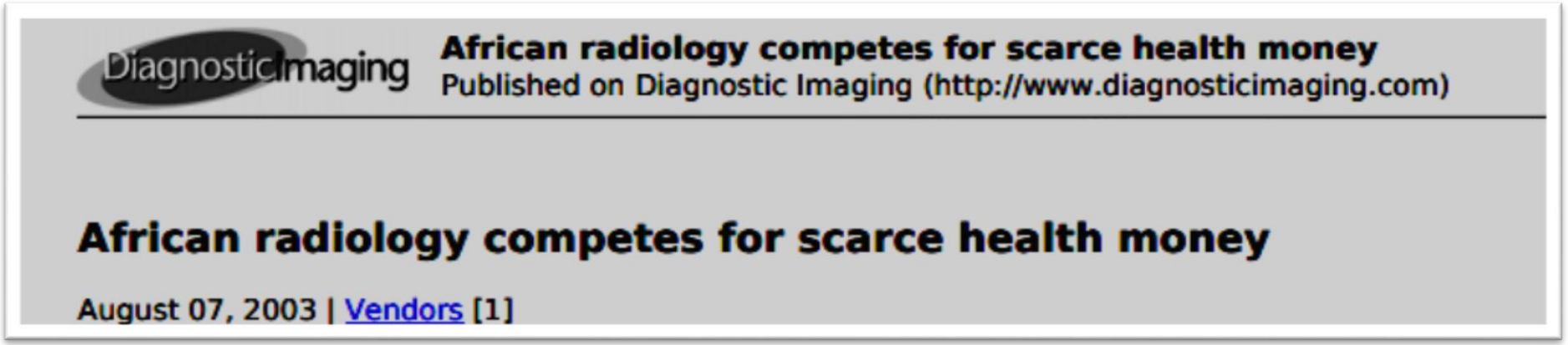
Status of OECD countries



Do we have adequate imaging facilities?



"We probably have **fewer than 400 radiologists** working in South Africa **for a population of 42 million**, and the majority of them actually work in private practice. There are probably **fewer than 50 radiologists** working **in the public health system**, which caters to the needs of almost **65% of the population**. ***Most hospitals in the public sector have never seen a radiologist***."

Dilemmas in including imaging for staging

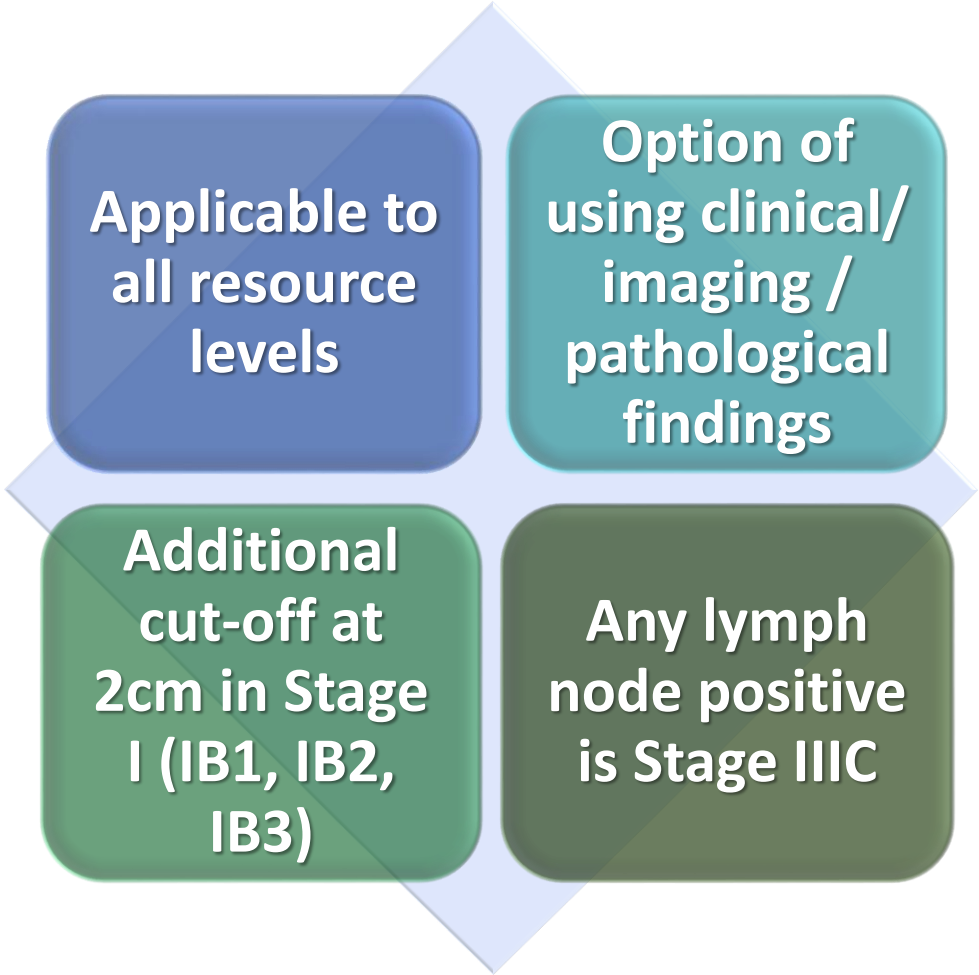
- Enlarged nodes in imaging may be infective
  - Especially true in HIV endemic areas
- Stromal invasion not confirmatory by imaging
- PET-CT also not confirmatory
- Confirmation needed by cytology / histology
- Will further increase the need for resources

CaCx Staging Revision 2018 – Process

Presented at FIGO 2018, Rio de Janeiro
FIGO Cancer Report 2018
Bhatla N et al. Int J Gynecol Obstet. 2018;143(Suppl 2):22-36.

Published
Bhatla N et al. Int J Gynecol Obstet. 2019.
https://doi.org/10.1002/ijgo.12749

CaCx Staging Revision 2018 – Salient Features



Int J Gynecol Obstet. 17 January 2019. https://doi.org/10.1002/ijgo.12749

Stage I

The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)

- **Stage IA** - Invasive carcinoma that can be diagnosed only by microscopy with measured deepest invasion < 5 mm[a] (lateral spread has been removed)

  Stage IA1 - Measured stromal invasion < 3.0 mm

  Stage IA2 - Measured stromal invasion ≥ 3.0 mm and < 5.0 mm

[a] The involvement of vascular/lymphatic spaces should not change the staging.

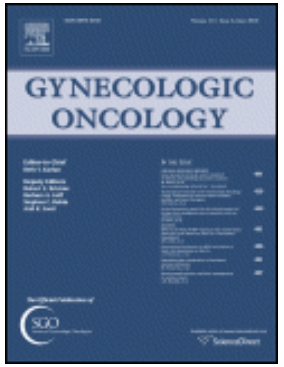
Stage I…

- **Stage IB -** Invasive carcinoma with measured deepest invasion ≥ 5 mm, limited to the cervix with size measured by maximum tumor diameter [a]

Stage IB1 - Invasive carcinoma ≥ 5.0 mm depth of invasion and < 2 cm in greatest dimension

Stage IB2 - Invasive carcinoma ≥ 2 cm and < 4 cm in greatest dimension

Stage IB3 - Invasive carcinoma ≥ 4 cm in greatest dimension



The vaginal radical trachelectomy: An update of a series of 125 cases and 106 pregnancies

Marie Plante *, Jean Gregoire, Marie-Claude Renaud, Michel Roy

Recurrences: 6 / 125 (4.8%)

Deaths : 2 / 110 (1.6%)

Risk factor associated with recurrence

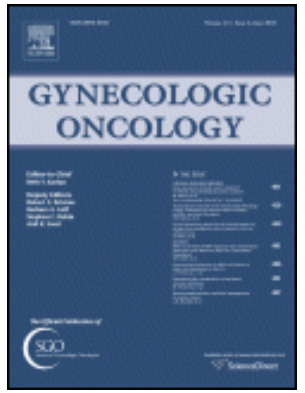
Size of the lesion > 2 cm (p = 0.001)

- 10% of patients had lesions > 2 cm
- Represented 50% of the recurrences

Plante M et al. Gynecol Oncol. 2011;121:290-297.

Vaginal Radical Trachelectomy for early stage cervical cancer. Results of the Danish National Single Center Strategy

L. Hauerberg [a,*], C. Høgdall [a], A. Loft [b], C. Ottosen [a], S.F. Bjoern [a], B.J. Mosgaard [a], L. Nedergaard [c], H. Lajer [a]

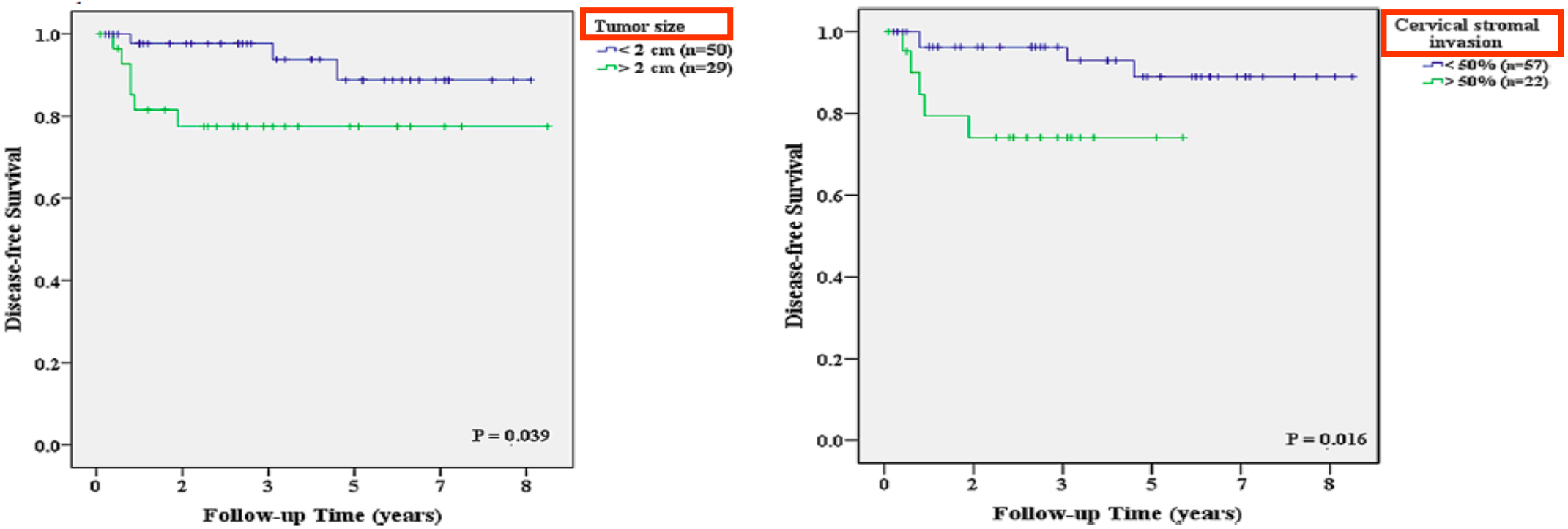


N=120
6 recurrences (5.1%); 2 deaths (1.7%)
7 patients had lesions >2 cm (5.8%)
3 recurrences (50%)

Hauerberg L, et al. Gynecol Oncol. 2015;138:304–310.

Long-Term Outcomes After Fertility-Sparing Laparoscopic Radical Trachelectomy in Young Women With Early-Stage Cervical Cancer: An Asan Gynecologic Cancer Group (AGCG) Study

JEONG-YEOL PARK, MD, PhD,[1] WON DEOK JOO, MD, PhD,[2] SUK-JOON CHANG, MD, PhD,[3]
DAE-YEON KIM, MD, PhD,[1] JONG-HYEOK KIM, MD, PhD,[1] YONG-MAN KIM, MD, PhD,[1]
YOUNG-TAK KIM, MD, PhD,[1] AND JOO-HYUN NAM, MD, PhD[1]*



Park JY et al. J Surg Oncol. 2014;110:252–257.

Evidence informing the change in Stage IB cut-offs

- Zhang Q, et al. Oncologic and obstetrical outcomes with fertility-sparing treatment of cervical cancer: a systematic review and meta-analysis. Oncotarget. 2017;8(28):46580-92. ***(Level I)***
- Póka R, et al. Intention-to-treat analysis of radical trachelectomy for early-stage cervical cancer with special reference to oncologic failures: single-institutional experience in Hungary. Int J Gynecol Cancer. 2017;27(7):1438-45. ***(Level II)***
- Tomao F, et al. Conization in early stage cervical cancer: Pattern of recurrence in a 10-year single-institution experience. Int J Gynecol Cancer. 2017;27(5):1001-8. ***(Level II)***

Controversial issues:

- *Presence of vascular/lymph space invasion:* Lymphovascular space invasion does not change the stage.
- *Extension to the uterine corpus*: Involvement of the uterine body does not change the stage.

Recommendations:

- The size and extent of the primary tumor can be assessed by clinical evaluation (pre- or intraoperative), imaging, and/or pathological measurement.

Stage II

Cervical carcinoma invades beyond the uterus, but not to the pelvic sidewall or to the lower third of the vagina

- **Stage IIA** Without parametrial invasion

  Stage IIA1 - Invasive carcinoma < 4 cm in greatest dimension

  Stage IIA2 - Invasive carcinoma ≥ 4 cm in greatest dimension

- **Stage IIB** With parametrial invasion

Controversial issues:

Use of imaging for assessment of parametrial involvement:

- The utility of imaging for evaluation of parametrium and upper vagina is less clear
- MRI performs better than CT scan for parametrial assessment
- False negative as well as false positive results have been reported especially when there is infection or with larger tumor size and stretching of the upper vagina by the growth

Stage III

The tumor extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or non-functioning kidney and/or involves pelvic and/or paraaortic nodes

Stage IIIA -Tumor involves lower third of the vagina, with no extension to the pelvic wall

Stage IIIB - Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney

Stage IIIC - Involves pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate to stage IIIC [b]).

Stage III C1 - Pelvic lymph node metastasis only

Stage III C2 - Paraaortic lymph node metastasis

[b] Example: Notation of r = imaging and p = pathology, e.g., imaging indicating pelvic lymph node metastasis would be Stage IIIC1r and by pathological findings would be Stage IIIC1p. When in doubt, the lower staging should be assigned.

Evidence informing the change – Imaging

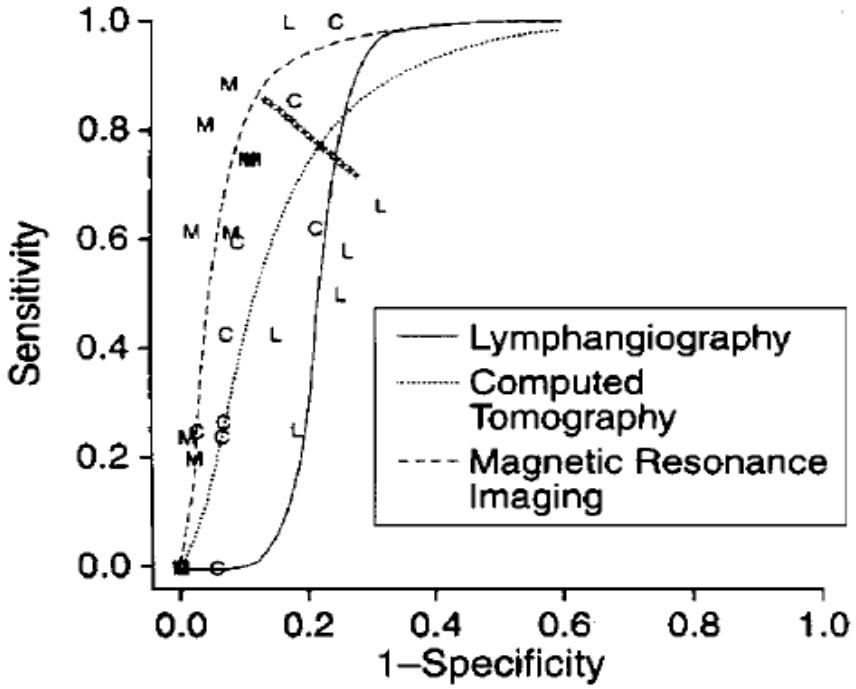
- Bipat S, et al. Computed tomography and magnetic resonance imaging in staging of uterine cervical carcinoma: a systematic review. Gynecol Oncol. 2003;91:59-66. ***(Level I)***
- Selman TJ, et al. Diagnostic accuracy of tests for lymph node status in primary cervical cancer: a systematic review and metaanalysis. CMAJ. 2008;178:855-62. ***(Level I)***
- Choi H, et al. Diagnostic performance of CT, MRI, and PET or PET/CT for detection of metastatic lymph nodes in patients with cervical cancer: Meta-analysis. Cancer Sci. 2010;101:1471-9. ***(Level I)***

MRI vs CT in cervix cancer staging?

Radiological Evaluation of Lymph Node Metastases in Patients With Cervical Cancer: A Meta-analysis

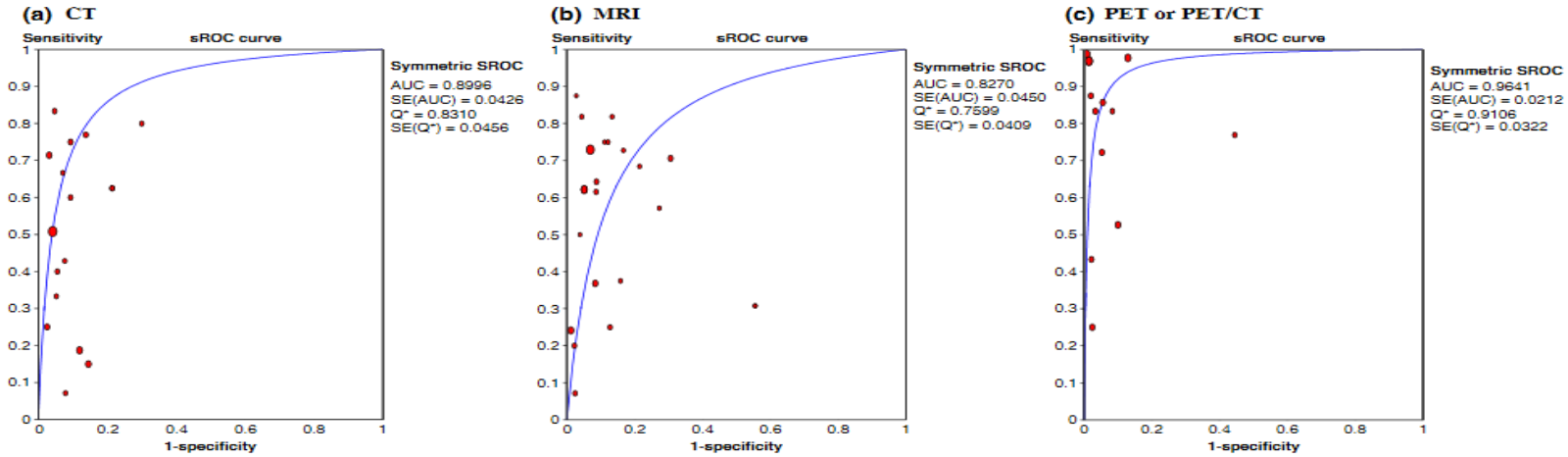
Scheidler J JAMA 1997;278:1096-1101.

- 17 studies comparing CT, MRI and LAG
- LAG, CT, and MR imaging perform similarly in the detection of lymph node metastasis from cervical cancer



MRI vs CT vs PET in cervix cancer staging?

- 41 studies with histologic confirmation



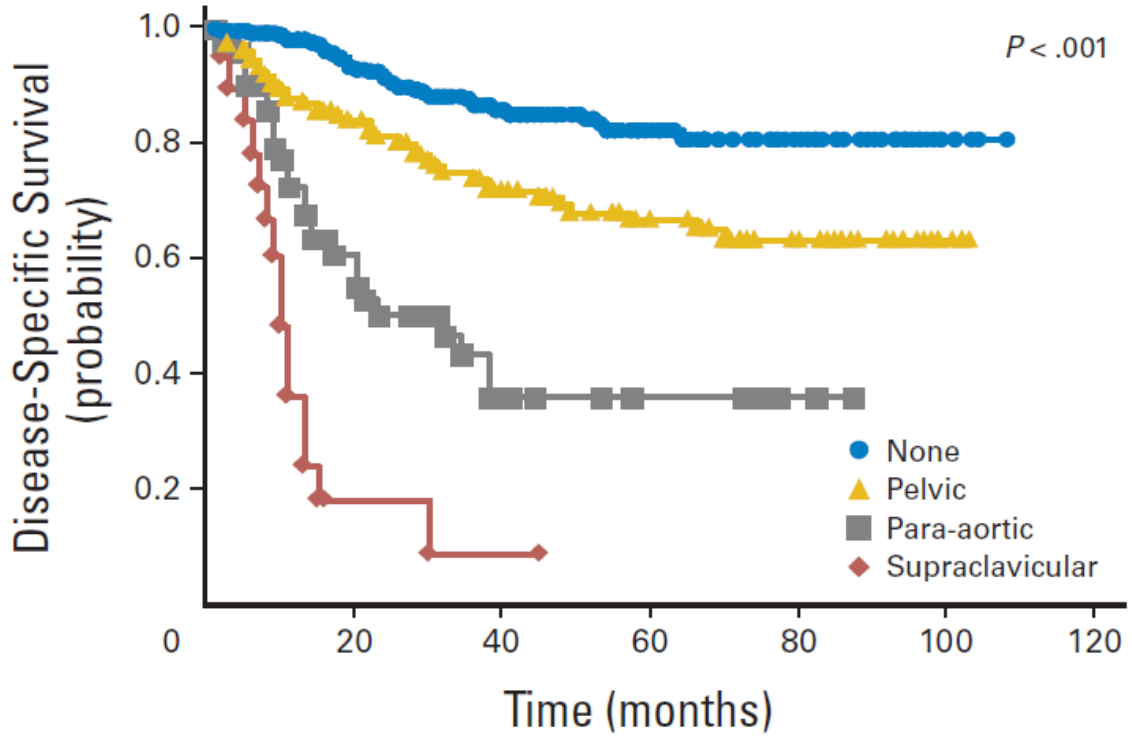
PET or PET/CT had an overall higher diagnostic performance than CT or MRI in detecting metastatic lymph nodes in patients with cervical cancer

Choi H, et al. Diagnostic performance of CT, MRI, and PET or PET/CT for detection of metastatic lymph nodes in patients with cervical cancer: Meta-analysis. Cancer Sci 2010;101:1471-9.

Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis

Elizabeth A. Kidd, Barry A. Siegel, Farrokh Dehdashti, Janet S. Rader, David G. Mutch, Matthew A. Powell, and Perry W. Grigsby

N =513



Stage I Ca Cervix

Kidd EA et al. J Clin Oncol. 2010;28:2108-2113.

Lymph Node Staging by Positron Emission Tomography in Cervical Cancer: Relationship to Prognosis

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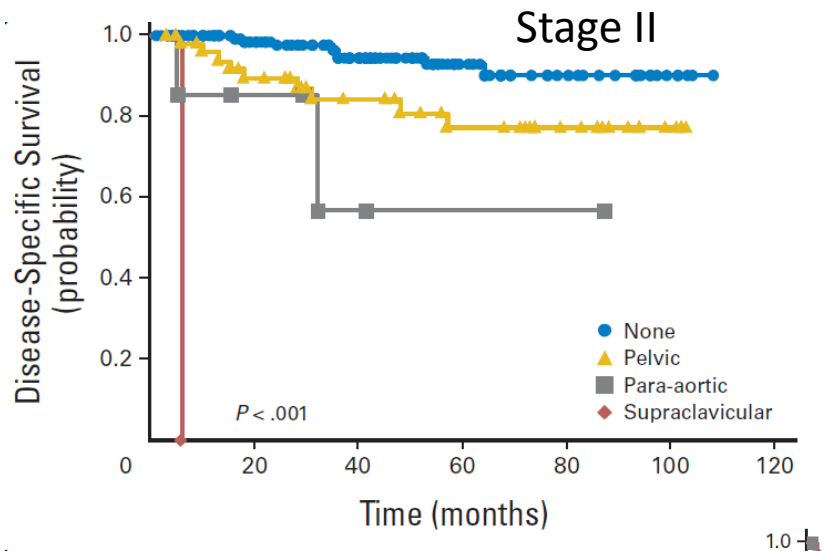

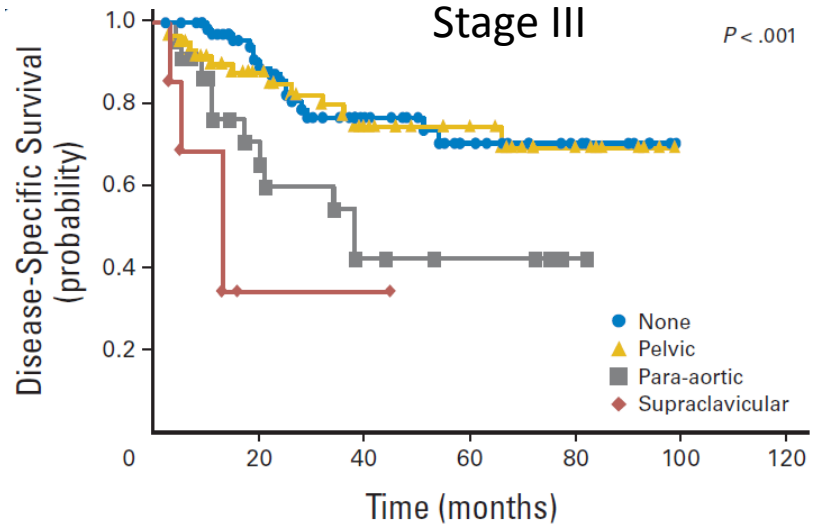

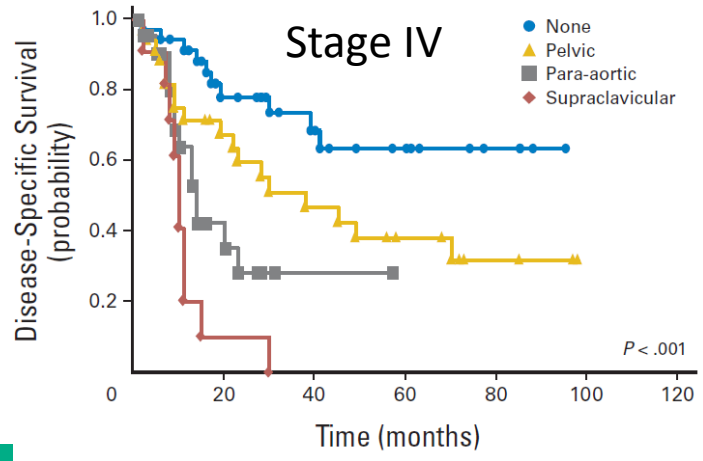

Kidd EA et al. J Clin Oncol. 2010;28:2108-2113.

Comparison of MRI and High-Resolution Transvaginal Sonography for the Local Staging of Cervical Cancer

TABLE 2
Diagnostic Accuracy of Disease Staging with MRI and TVS in the Detection of Stromal Invasion in 46 Women with Invasive Cervical Cancer

	Histopathologically Positive, n	Histopathologically Negative, n	
MRI positive	12	9	Sensitivity, 80% Specificity, 50% Positive predictive value, 57% Negative predictive value, 75% Kappa, 0.29 ("fair")
MRI negative	3	9	
TVS positive	12	9	Sensitivity, 80% Specificity, 50% Positive predictive value, 57% Negative predictive value, 75% Kappa, 0.29 ("fair")
TVS negative	3	9	

Moloney F, et al. J Clin Ultrasound. 2016

Comparison of MRI and High-Resolution Transvaginal Sonography for the Local Staging of Cervical Cancer

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Diagnostic Accuracy of Disease Staging with MRI and TVS in the Detection of Parametrial Invasion in 46 Women with Invasive Cervical Cancer

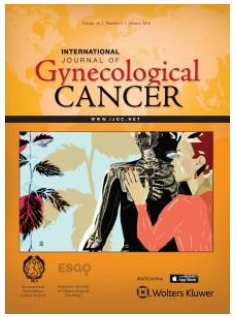
	Histopathologically Positive, n	Histopathologically Negative, n	
MRI positive	2	4	Sensitivity, 40% Specificity, 86% Positive predictive value, 33% Negative predictive value, 89% Kappa, 0.238 ("fair")
MRI negative	3	24	
TVS positive	1	3	Sensitivity, 20% Specificity, 89% Positive predictive value, 25% Negative predictive value, 86% Kappa, 0.101 ("poor")
TVS negative	4	25	

Conclusion: TVS performed by a dedicated gynecologic radiologist is a feasible and economic imaging modality with a diagnostic accuracy comparable to MRI.

Moloney F, et al. J Clin Ultrasound. 2016

Transrectal ultrasound and magnetic resonance imaging in staging of early cervical cancer

D. FISCHEROVA*, D. CIBULA*, H. STENHOVA†, H. VONDRICHOVA†, P. CALDA*, M. ZIKAN*, P. FREITAG*, I. SLAMA*, P. DUNDR‡ & I. BELACEK§



Accuracy of MRI and TRUS in the identification of tumor ($P \leq 0.006$) in the whole group ($n = 95$) and in the subgroup of small tumors ≤ 1 cm^3 ($P \leq 0.049$)

Imaging modality		Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
TRUS	95 patients	93.42 (85.31–97.83)	94.74 (73.97–99.87)	98.61 (92.50–99.96)	78.26 (56.30–92.54)	93.68 (86.76–97.65)
	≤ 1 cm^3	72.00 (50.61–87.93)	97.14 (90.06–99.65)	90.00 (68.30–98.77)	90.67 (81.71–96.16)	90.53 (82.78–95.58)
MRI	95 patients	82.89 (72.53–90.57)	84.21 (60.42–96.62)	95.45 (87.29–99.05)	55.17 (35.69–73.55)	83.16 (74.10–90.06)
	≤ 1 cm^3	44 (24.40–65.07)	94.29 (86.01–98.42)	73.33 (44.90–92.21)	82.50 (72.38–90.09)	81.05 (71.72–88.37)

PPV, positive predictive value; NPV, negative predictive value.

Accuracy of MRI and TRUS in the evaluation of parametrial involvement ($P \leq 0.219$)

Imaging modality	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Accuracy, % (95% CI)
TRUS	83.33 (35.88–99.58)	100.00 (95.94–100)	100.00 (47.82–100)	98.89 (93.96–99.97)	98.95 (94.27–99.97)
MRI	50.00 (11.81–88.19)	97.75 (92.12–99.73)	60.00 (14.66–94.73)	96.67 (90.57–99.31)	94.74 (88.14–98.27)

PPV, positive predictive value; NPV, negative predictive value.

Int J Gynecol Cancer. 2008;18:766-772.

THREE-DIMENSIONAL TRANSVAGINAL TOMOGRAPHIC ULTRASOUND IMAGING FOR CERVICAL CANCER STAGING

XUE-SONG HAN,* CHUN-PING NING,† LI-TAO SUN,* XIAO-YING LI,* YAN-QING PENG,* and MEI-ZHENG DANG*

- N=80
- Tomographic transvaginal US

Table 3. Comparison of clinical, US and MRI staging

		Clinical staging			US staging			MRI staging		
Stage	Final staging	Accurate	Under-staged	Over-staged	Accurate	Under-staged	Over-staged	Accurate	Under-staged	Over-staged
IA	5	5	—	—	1	2	2	0	3	2
IB	50	42	2	6	48	—	2	45	1	4
IIA	15	13	—	2	15	—	—	15	—	—
IIB	10	3	5	2	10	—	1	6	2	2
Accuracy		(63/80) 78.75%			(74/80) 92.50%			66/80 (82.50%)		
Comparisons										
Clinical vs. US					$\chi^2 = 4.902, p = 0.022$					
US vs. MRI					$\chi^2 = 2.686, p = 0.079$					

US = ultrasound; MRI = magnetic resonance imaging.

Han XS, et al. Ultrasound Med Biol. 2015

Controversial issues in Stage III

- *Presence of isolated tumor cells (ITCs) or micrometastases;*
  - Metastases in lymph nodes have been graded as ITCs (<0.2 mm), micrometastases (0.2-2.0 mm) or macrometastases (>2.0 mm).
  - Presence of ITCs or micrometastases signifies low volume metastasis; their implication is not clear. Their presence may be recorded but does not change the stage.
- *Differentiating metastases from infection:*
  - Many countries with a high cervical cancer burden also have a high prevalence of tuberculosis and HIV. In these endemic areas, nodes may be enlarged without metastases. The assessment of metastatic lymph nodes versus infected lymph nodes does not have clear radiological criteria.

Controversial issues in Stage III

- *Sentinel lymph nodes:*
  - Sentinel lymph node dissection is commonly used in vulvar and endometrial cancer.
  - In cervical cancer, good sensitivity and specificity has been reported with acceptable false negative rates.
  - Following the protocol is essential for this procedure. Appropriate facilities and expertise should be available to validate and follow the protocol for the sentinel lymph node approach, which also requires good backup of pathology for ultrastaging and immunohistochemistry.

Recommendations

- Surgicopathological assessment of lymph node involvement, whether by conventional or MIS route, requires advanced surgical skills.
- 85% of cases occur in low resource settings, where the required professional skills and infrastructure facilities are presently not widely available.
- Pathological confirmation is the gold standard but imaging can be used to interpret disease extent.
- The choice of imaging modality for nodal evaluation has not been fixed by FIGO. It depends upon availability and patients' affordability. Non-availability of an imaging modality should not be a reason for undue delay in initiation of treatment.

Recommendations (contd.)

- FIGO does not define criteria to discriminate between malignancy and inflammation / infection on imaging. The clinician must opine on whether these look suspicious enough to upstage the case or not.
- Clinical assessment of staging or use of other facilities as available is permissible.
- The best available technology should be used for assessment, and the lowest appropriate stage should be assigned, i.e., when in doubt assign the lower stage.
- The method of assigning the stage is to be recorded and reported.

Imaging & Pathology Recommendations

- FIGO recommends adding imaging and pathological findings, collection and analysis of these data.
- A parenthetical notation of ‘r” and ‘p’ would be added.
  - r = Radiological (imaging) findings
    - cross-sectional imaging, e.g., US, CT, MRI, PET, PET/CT scans
  - p = Pathological findings
    - biopsy and/or FNAC proven findings

Stage IV

Stage IV The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum.

Stage IVA Spread of the growth to adjacent organs

Stage IVB Spread to distant organs

Summary of revisions (2018)

- Allowing the use of any imaging modality and/or pathological findings for allocating stage, in addition to the previous option of clinical staging. Recording ‘r’ or ‘p’ to indicate resource used.
- In stage I, amendments to microscopic pathological findings and size designations, and allowing the use of imaging and/or pathological assessment of the size of the cervical tumor.
- In stage II, allowing the use of imaging and/or pathological assessment of the size of the cervical tumor and parametrial invasion.
- In stages I through III, allowing assessment of retroperitoneal lymph nodes by imaging and/or pathological findings, and, if deemed metastatic, the stage is designated stage IIIC.
- Removing previous recommendations for routine investigations.

LACC TRIAL – MIS IN CaCx

Approach to Early Stage Cervical Cancer

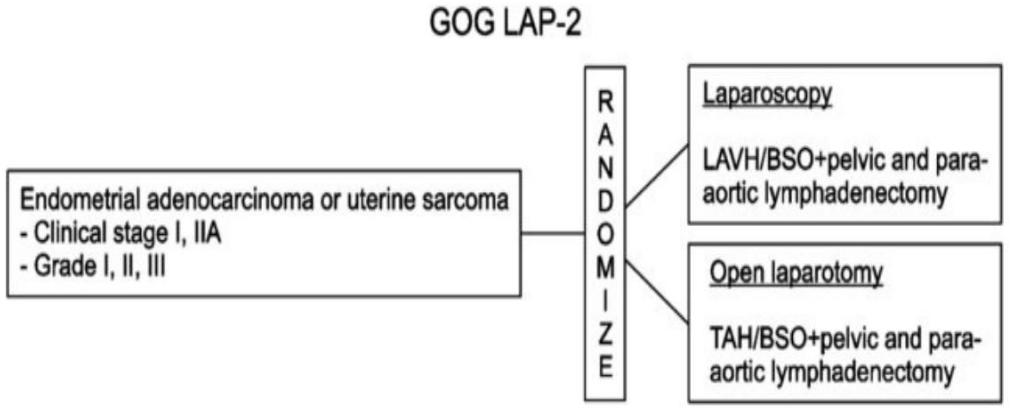
- Is surgery or radiotherapy better?
- Landmark trial, Landoni et at
  - Randomized 343 patients, IB-IIA to either
    - Radical hysterectomy
    - External beam radiotherapy (pelvic RT)
    - 5-year outcome: no difference; Non-bulky: OS surgery 87% vs. RT 90% (NS), DFS surgery 80% vs. 82% (NS)
    - AdenoCA: significantly better outcomes with surgery; OS (70% vs. 59%), DFS (66% vs. 47%)
    - Complications (Grade 2-3): Surgery 28% vs RT 12% (SS). Severe leg edema surgery 0%, RT 1%, surgery + RT 9%

Source: Landoni et al Lancet. 1997 23;350(9077):535-40

Key is identifying patients that have surgically resectable disease that done require adjuvant treatment

Minimally Invasive Surgery in Gyne Cancer

- Minimally invasive surgery is now an accepted and “standard of care” approach to endometrial cancer staging.
- Several studies have shown the benefit of using this technique for appropriate detection for advanced and occult metastatic disease
- The LAP2 trial showed that a MIS surgery approach was appropriate for the detection of occult disease at that survival was similar to open methods with lower complication rates



Original Article

Minimally Invasive Radical Hysterectomy for Cervical Cancer Is Associated With Reduced Morbidity and Similar Survival Outcomes Compared With Laparotomy

Elisabeth Diver, MD, Emily Hinchcliff, MD, Allison Gockley, MD, Alexander Melamed, MD, Leah Contrino, PA-C, Sarah Feldman, MD, MPH, and Whitfield Growdon, MD*

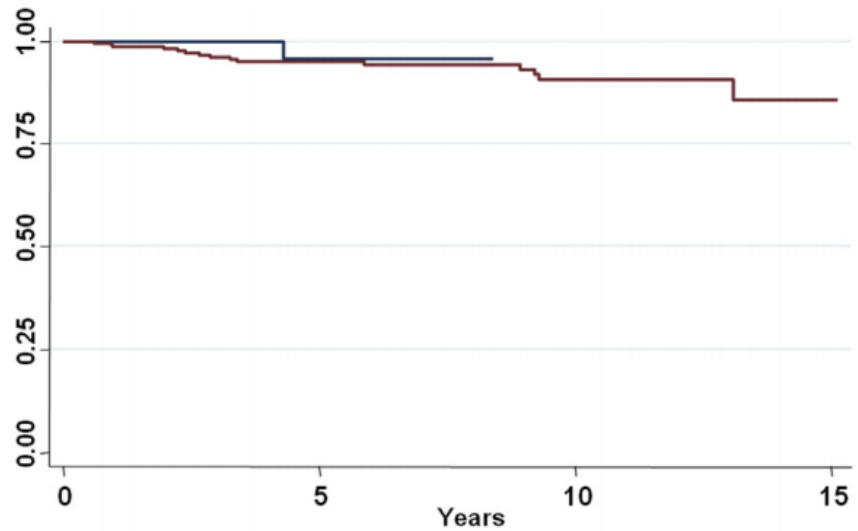
Table 3

Patient outcomes by surgical modality

Outcome	MIS (n = 101)	XL (n = 282)	p value
Any chemotherapy, n (%)	17 (16.7)	60 (21.3)	.32
Any radiation therapy, n (%)	20 (19.8)	69 (24.5)	.28
Recurrence, n (%)	5 (5.0)	18 (6.4)	.86
Survival, yr, median	Not reached	Not reached	.29

Fig. 2

Overall survival for 383 patient cohort that underwent RH for early-stage cervical carcinoma. This Kaplan-Meier graph depicts the overall survival for women in our cohort stratified by mode of surgical procedure. Because MIS techniques were introduced in later eras, the duration of follow-up was shorter for the MIS group. There was no statistical difference between the 2 groups (log-rank p = .29).



What about randomized data in cervical cancer?

- To answer this question in cervical cancer, a randomized trial similar to the LAP-2 data was needed
- Several constraints on examination of this data….
  - The development of new technologies as comapred to LAP-2 trial (mainly l-scope and no robotic surgery)
  - The advent of sentinel lymph node mapping for staging in both endometrial and possibly cervical cancer
  - Centralized evaluation of the surgical technique
  - Is robotic surgery better than standard straight-stick approaches?
  - International spread of MIS technologies...

ORIGINAL ARTICLE

Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer

Pedro T. Ramirez, M.D., Michael Frumovitz, M.D., Rene Pareja, M.D., Aldo Lopez, M.D., Marcelo Vieira, M.D., Reitan Ribeiro, M.D., Alessandro Buda, M.D., Xiaojian Yan, M.D., Yao Shuzhong, M.D., Naven Chetty, M.D., David Isla, M.D., Mariano Tamura, M.D., Tao Zhu, M.D., Kristy P. Robledo, Ph.D., Val Gebski, M.Stat., Rebecca Asher, M.Sc., Vanessa Behan, B.S.N., James L. Nicklin, M.D., Robert L. Coleman, M.D., and Andreas Obermair, M.D.

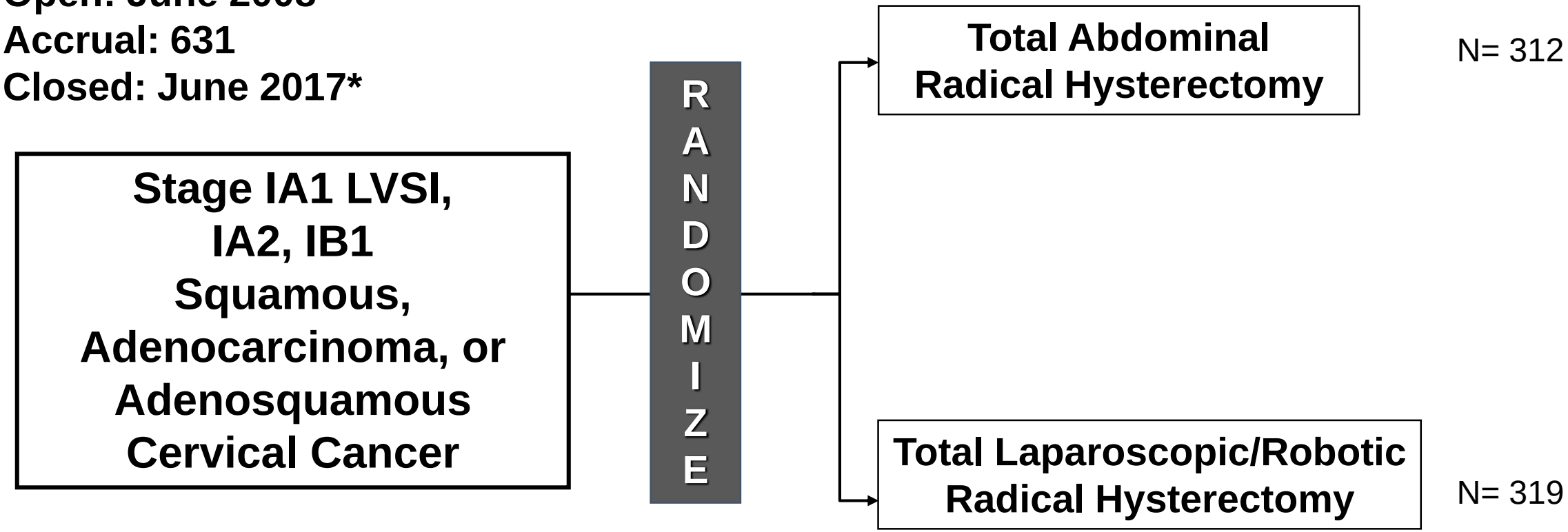
ORIGINAL ARTICLE

Survival after Minimally Invasive Radical Hysterectomy for Early-Stage Cervical Cancer

Alexander Melamed, M.D., M.P.H., Daniel J. Margul, M.D., Ph.D., Ling Chen, M.D, M.P.H., Nancy L. Keating, M.D., M.P.H., Marcela G. del Carmen, M.D., M.P.H., Junhua Yang, M.S., Brandon-Luke L. Seagle, M.D., Amy Alexander, M.D., Emma L. Barber, M.D., Laurel W. Rice, M.D., Jason D. Wright, M.D., Masha Kocherginsky, Ph.D., Shohreh Shahabi, M.D., E.M.H.A., and J. Alejandro Rauh-Hain, M.D., M.P.H.

LACC Study Schema

Open: June 2008
Accrual: 631
Closed: June 2017*



*Recommendation of study termination by DSMC

LACC Trial Objectives

Primary: Disease Free Survival

Secondary: Overall Survival

Patterns of Recurrence

Treatment-Associated Morbidity

Cost-Effectiveness

Pelvic floor Dysfunction

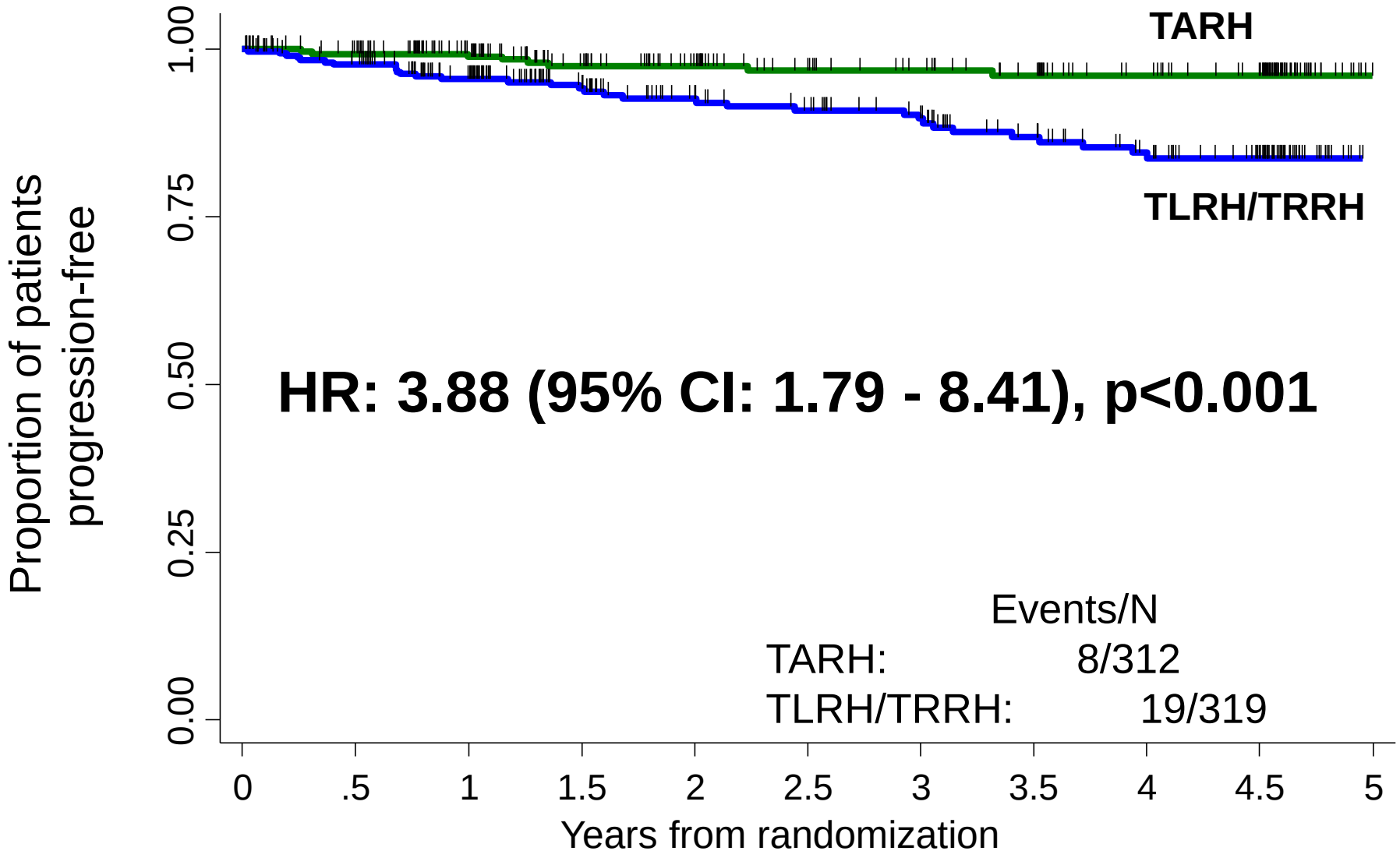
Feasibility of Sentinel Nodes

Quality of Life

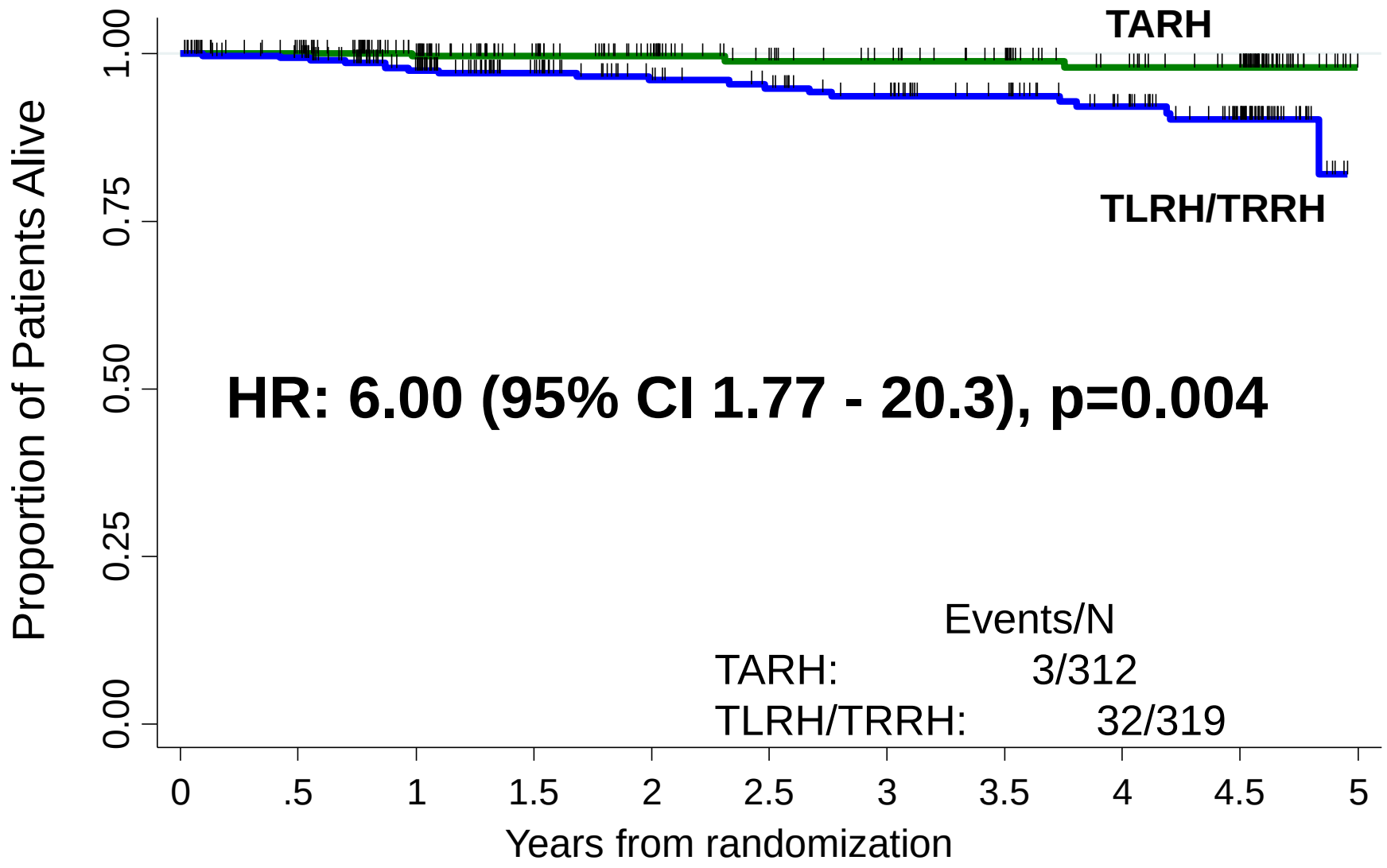
Demographics

	Open	MIS
Characteristic	**(n=312)**	**(n=319)**
Mean age, yr (SD)	46.0 (10.6)	46.1 (11.0)
Mean BMI, kg/m^2 (SD)	26.2 (5.3)	27.2 (5.6)
Geographic Region, n (%)		
Asia	63 (20)	63 (20)
Australia/New Zealand	48 (15)	46 (14)
Europe	27 (9)	32 (10)
North America	49 (16)	45 (14)
South America	125 (40)	133(42)
Type of incision, n (%)		
Vertical midline	156 (50)	
Low transverse	118 (38)	
Did not undergo open surgery	38 (12)	

Progression-Free Survival (PFS)



Overall Survival (OS)



Where does this leave MIS surgery in all of this?

- Randomized data now show both PFS and OS are impaired after MIS approach for cervical cancer.
- HR for PFS (recurrence) is nearly 4X with MIS approach.
- Risk of death from cervical cancer after MIS procedures is 6 times greater.
- This is a well done randomized trial
  - Centralized surgical review at top cancer institutes
  - Both groups appear to be equally balanced
  - Number of nodes and parametrial dissection appear to be equivocal
  - Blinded statistical evaluation

So why the discrepancy……

- Surgical technique: ? parametrial dissection not as extensive as in open techniques; Most surgeons do not undergo a centralized review of their parametrial dissection/margin (2 cm)
- Vaginal resection and margin: Did surgeons get an adequate surgical margin on the vaginal specimen?
- Internal prejudice in previous data - many retrospective, single institution data sets suffer from well known issues in retrospective studies (bias, inclusion/exclusion criteria, coding errors etc.)
- Lack of international participation in previous studies…

Conclusions after LACC…….

- MIS approaches to cervical cancer appear to have increased risk of recurrence and decreased overall survival
- Extensive discussion with patients about possible risks of MIS approaches over standard techniques must be had in the interest of ethics and patient autonomy.
- Many practitioners in the US and elsewhere have now switched back to open radical hysterectomy and the technique should be continued to be taught to trainees and future.
- Presently MIS to be performed in research settings only

NATIONAL PROGRAMME

The National Programme for the Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) scheme, launched in 2010, is being implemented as part of the National Health Mission (NHM).

Prevention, Screening and Control of Common Non-Communicable Diseases:

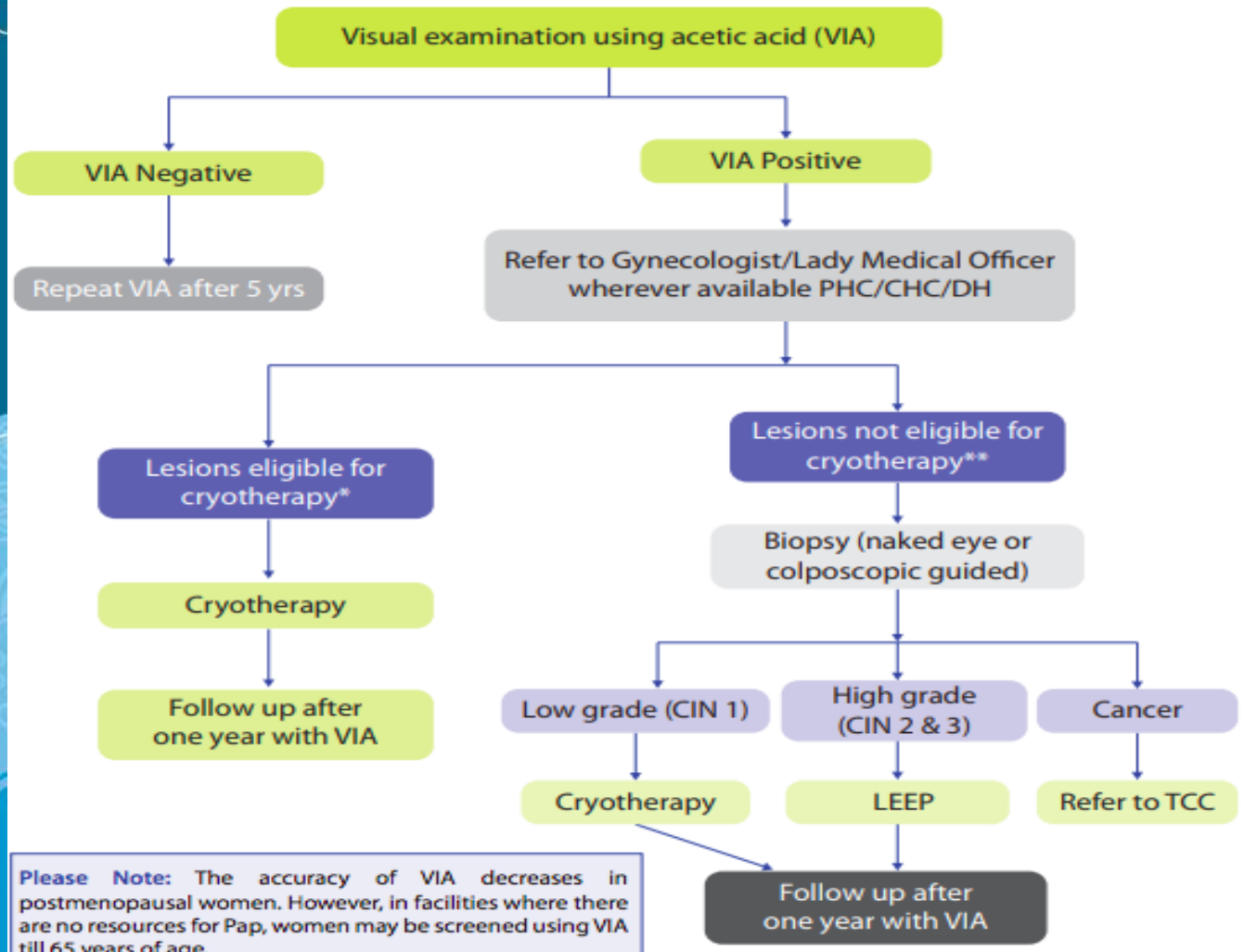
Hypertension, Diabetes and Common Cancers (Oral, Breast, Cervix)

(Part of Comprehensive Primary Health Care)

2016

Screen and Treat

Annexure 1b: Screening and Management Algorithm for Cervical cancer



Please Note: The accuracy of VIA decreases in postmenopausal women. However, in facilities where there are no resources for Pap, women may be screened using VIA till 65 years of age.

***Eligibility for cryotherapy:**

- The lesion should not be spread over more than 2 quadrant of cervix
- The entire lesion is located in the ectocervix without extension to the vagina and/or endocervix
- The lesion is visible in its entire extent
- The lesion can be adequately covered by the largest available cryotherapy probe
- There is no suspicion of invasive cancer

****Cryotherapy not recommended if:**

Symptoms:

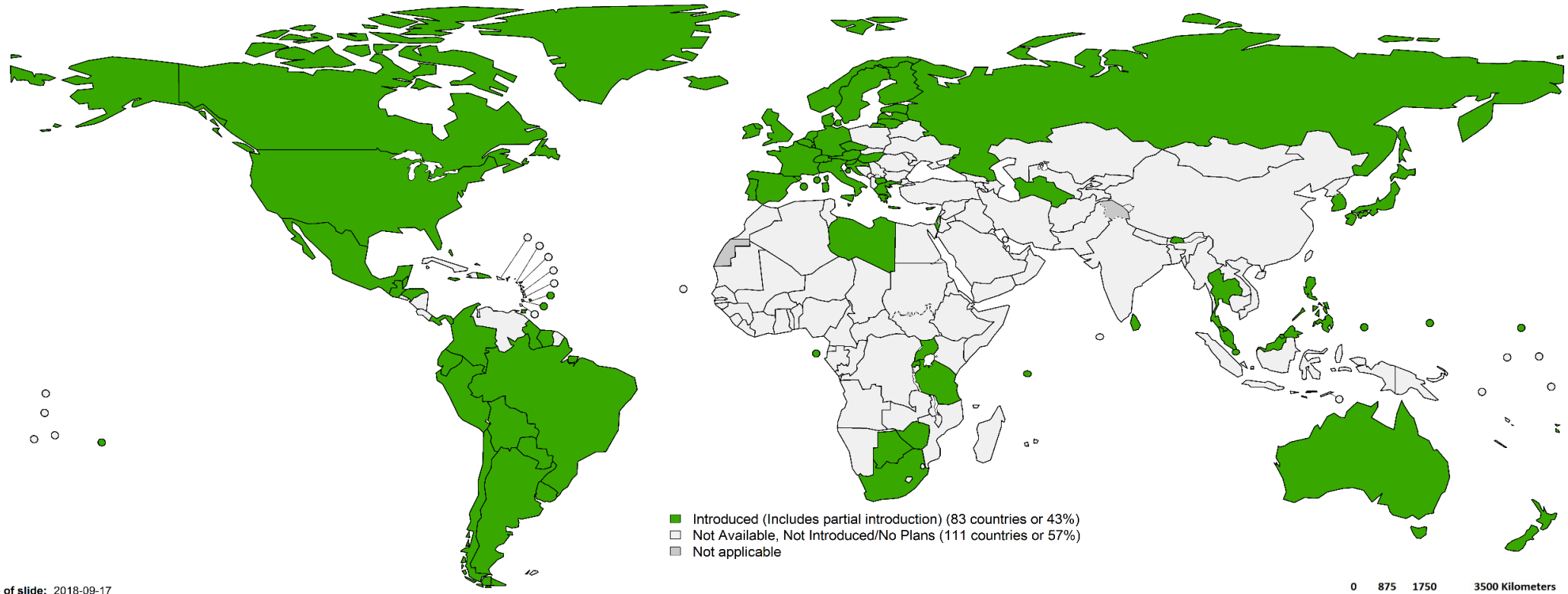
1. Postcoital bleeding
2. Postmenopausal bleeding

Examination:

3. Overt cervical growth
4. Irregular surface
5 Bleeds on touch

85 countries introduced HPV vaccine by Oct. 2018

Countries with HPV vaccine in the national immunization programme



Date of slide: 2018-09-17
Map production: Immunization, Vaccines and Biologicals (IVB), World Health Organization(WHO)
Data source: IVB database, as at 17/09/2018

Disclaimer:

The boundaries and names shown and the designations used on this map do notimply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area nor of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

World Health Organization

Progress in HPV vaccination

- Approved by NTAGI
- Delhi launched the vaccine program for school girls aged 11 years in 2016
- Punjab launched in Nov 2016
  - CHC based program
  - Class 6 students
  - Allows opt-in approach
- Sikkim in 2018

Cost Rica Vaccine Trial: Vaccine efficacy by number of doses after 4-yrs FU

Women ages 18-25 years;

Endpoint: HPV16/18 infections that persist for 6+ months

# of Doses	Vaccine Arm	# Women	# (%) with endpoint	HPV16/18 VE (95%CI)
3	Control	3010	229 (7.6%)	**84% (77% to 89%)**
	HPV	2957	37 (1.3%)	
2	Control	380	24 (6.3%)	**81% (53% to 94%)**
	HPV	422	5 (1.2%)	
1	Control	188	15 (8.0%)	**100% (79% to 100%)**
	HPV	196	0 (0%)	

p trend= 0.2

Kreimer AR et al JNCI, 2011

IARC 2- vs 3- dose HPV Vaccine multi-centric clinical trial – Study Sites

World Health Organization (WHO)
International Agency for Research on Cancer (IARC)
Lyon, France

In collaboration with

TMH-Mumbai

NDMCH-Barshi

JCDC-Pune

CFCHC-Ambillikai

GCRI-Ahmedabad

AIIMS-New Delhi

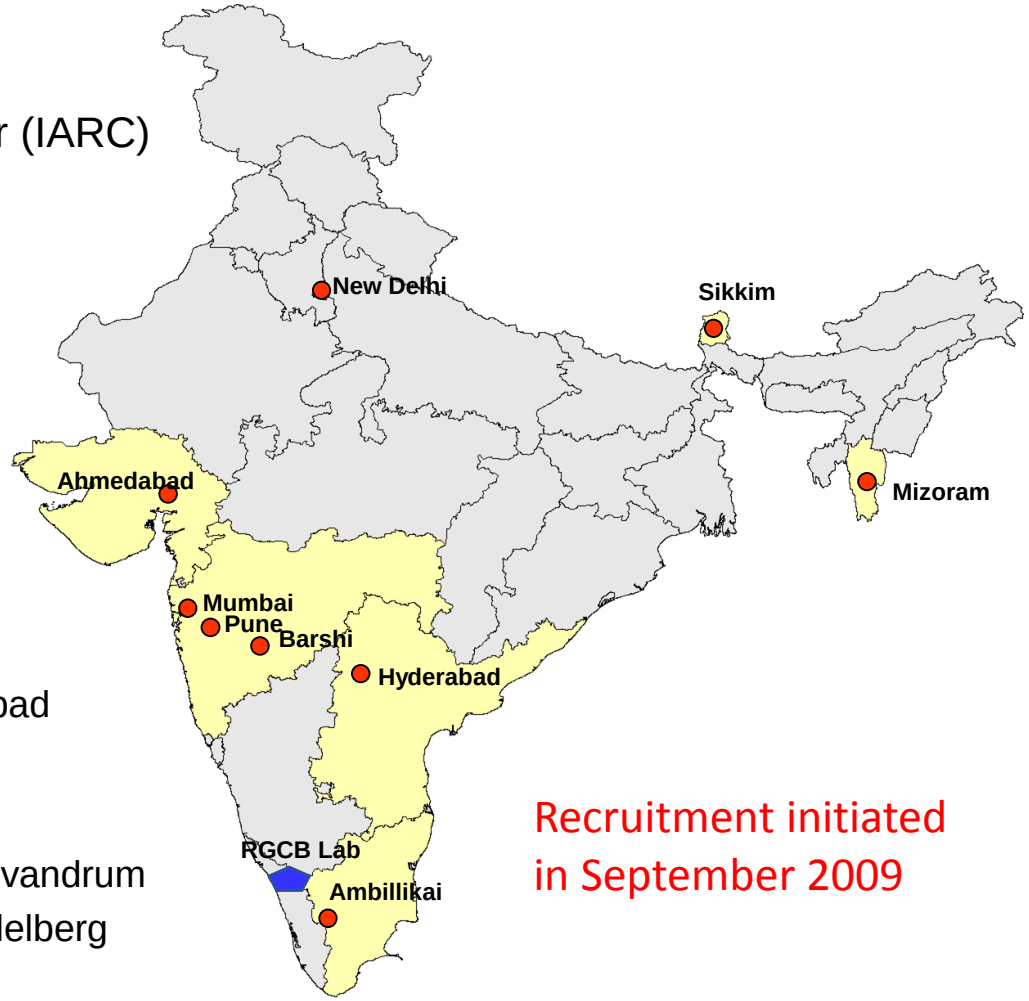
MNJ Institute of Oncology and RCC, Hyderabad

Cancer Foundation of India (CFI), Kolkata

and

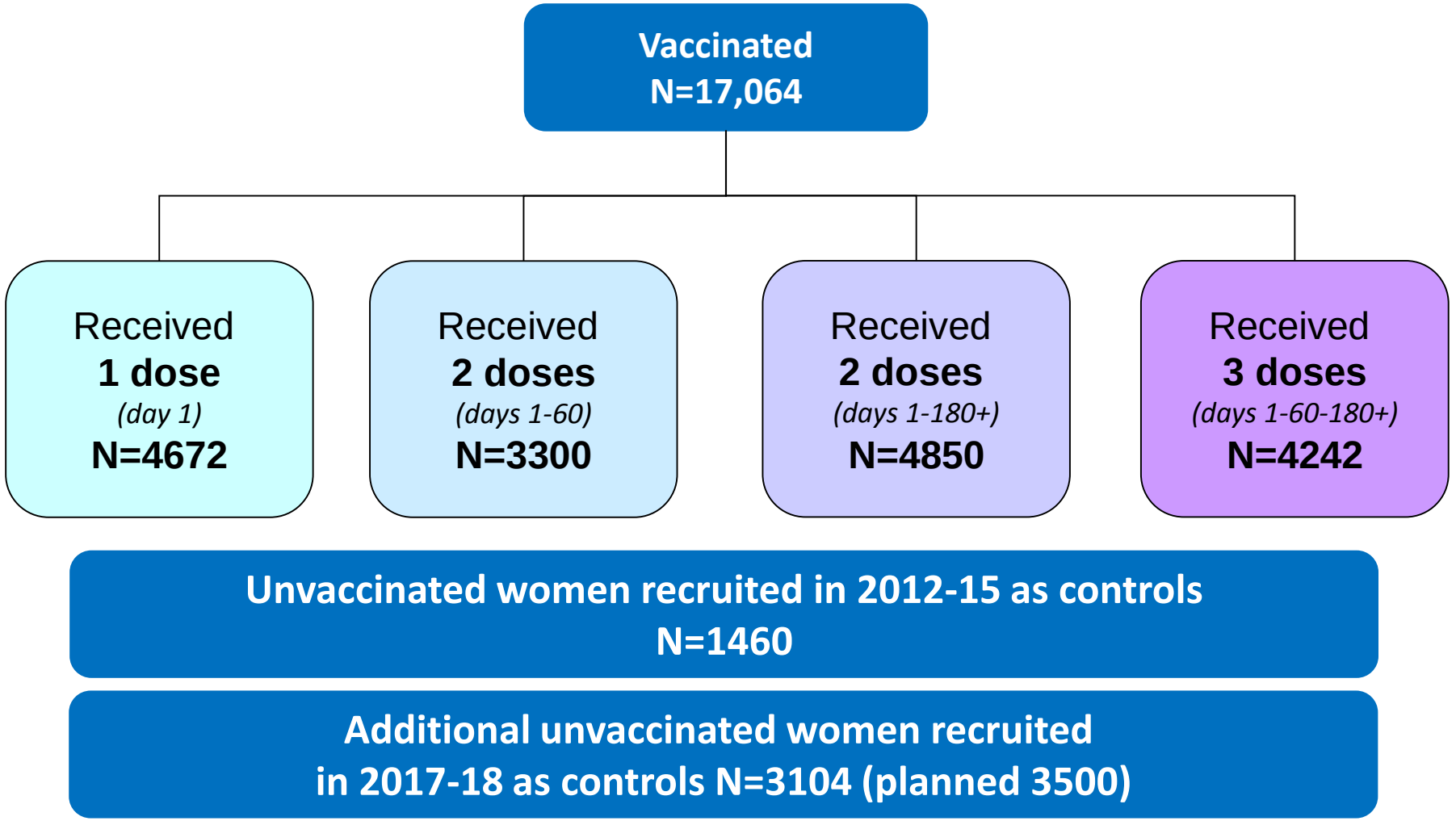
Rajiv Gandhi Centre for Biotechnology (RGCB), Trivandrum

German Cancer Research Institute (DKFZ), Heidelberg



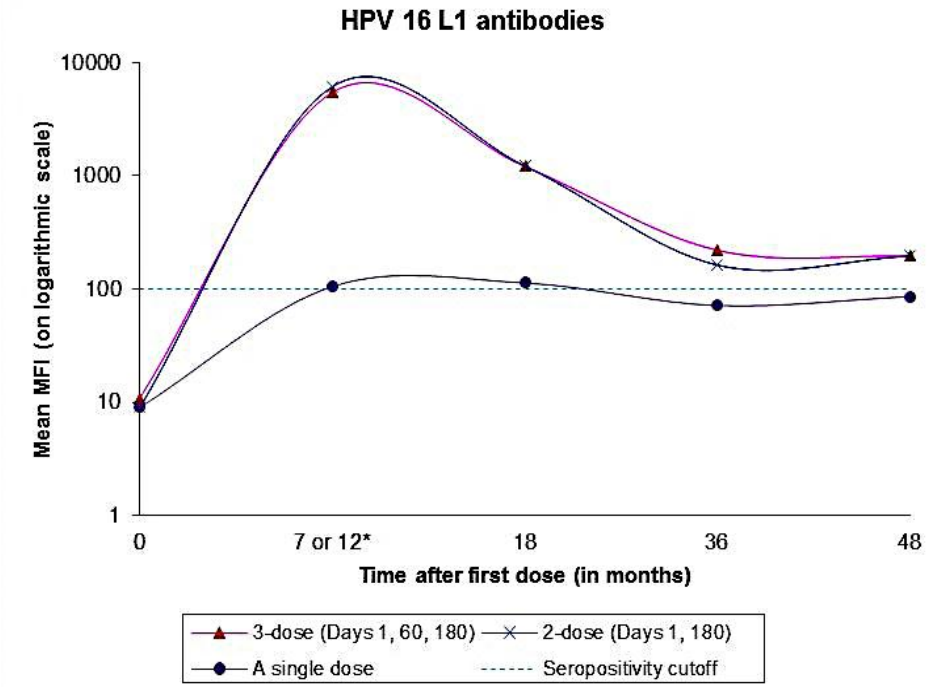
Recruitment initiated in September 2009

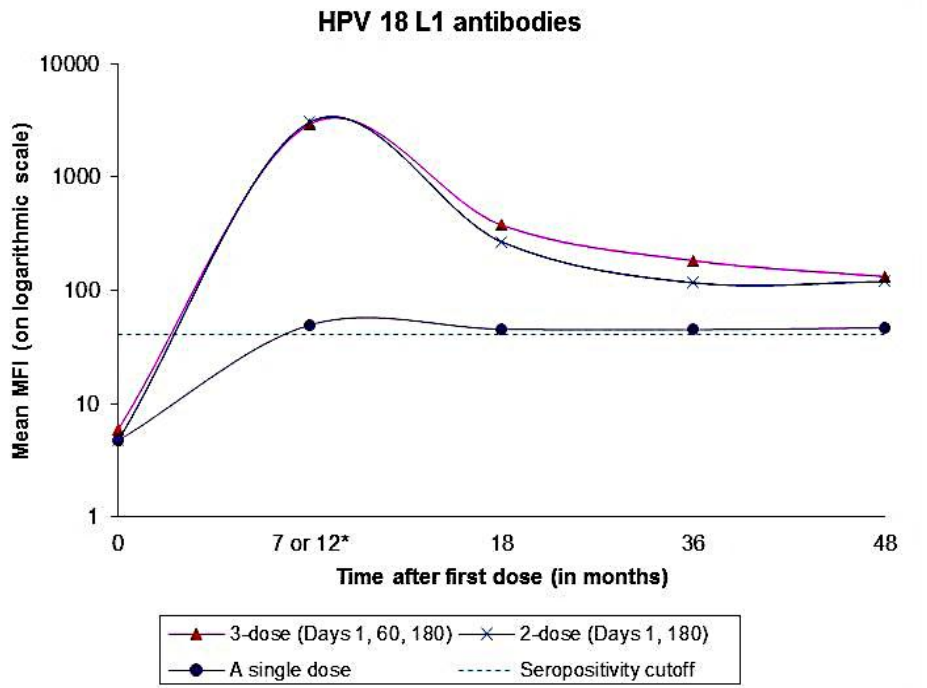
No. of girls/women (10-18 year at recruitment) by Vaccine Dose Groups (All study sites) in the FU Study



Total Antibody Titres against HPV 16/18

Mean MFI values for HPV 16 and 18 L1 antibodies at different time points among girls who completed vaccination per protocol (vaccination days 1, 60 and 180 (3-dose group) or days 1 and 180 (2-dose group)), and those who received only a single dose of vaccination





No difference in titres between 10-14 and 15-18 year olds

Dose received	Samples tested				
	Day 1	Month 7 or 12	Month 18	Month 36	Month 48
3-dose (Days 1, 60, 180)		308	313	271	239
2-dose (Days 1, 180)		317	314	278	243
A single dose		528	476	510	397
Total	1937	1153	1103	1059	879

Sankaranarayanan R, et al. Lancet Oncol. 2016;17(1):67-77.

INCIDENCE of HPV infections
(targeted & non-targeted types, N=9,000)

Study Group	Women assessed (N)	Incident HPV 16/18 infection N (%)		Incident HPV 31/33/45 infection N (%)		Incident non-targeted excluding HPV 31/33/45 infection N (%)	
All vaccinated	7516	149	(2.0)	327	(4.4)	1149	(15.3)
Unvaccinated	1484	120	(8.1)	132	(8.9)	339	(22.8)
3- dose (Days 1, 60 & 180+)	1637	29	(1.8)	75	(4.6)	270	(16.5)
2- dose (Days 1 & 180+)	1662	27	(1.6)	74	(4.5)	252	(15.2)
2- dose (Days 1 & 60+)	1799	42	(2.3)	57	(3.2)	238	(13.2)
1- dose	2418	51	(2.1)	121	(5.0)	389	(16.1)

PERSISTENCE of HPV infections
(targeted & non-targeted types, N=6,259)

Study Group	Women assessed (N)	Persistent HPV 16/18 infection N (%)		Persistent HPV 31/33/45 infection N (%)		Persistent non-targeted excluding HPV 31/33/45 infection N (%)	
All vaccinated	5017	6	(0.1)	24	(0.5)	136	(2.7)
Unvaccinated	1242	28	(2.3)	12	(1.0)	57	(4.6)
3- dose (Days 1, 60 & 180+)	1056	1	(0.1)	4	(0.4)	31	(2.9)
2- dose (Days 1 & 180+)	1055	1	(0.1)	8	(0.8)	31	(2.9)
2- dose (Days 1 and 180+)	1263	3	(0.2)	2	(0.2)	27	(2.1)
1- dose	1643	1	(0.1)	10	(0.6)	47	(2.9)

Conclusions – HPV Vaccination

- Emerging data suggest the two-dose schedule can be extended till 18 years age
- One-dose schedule may afford equivalent protection – RCT is under way
- Vaccination of older women is licensed though the protection will be less than for younger women

World Health Organization

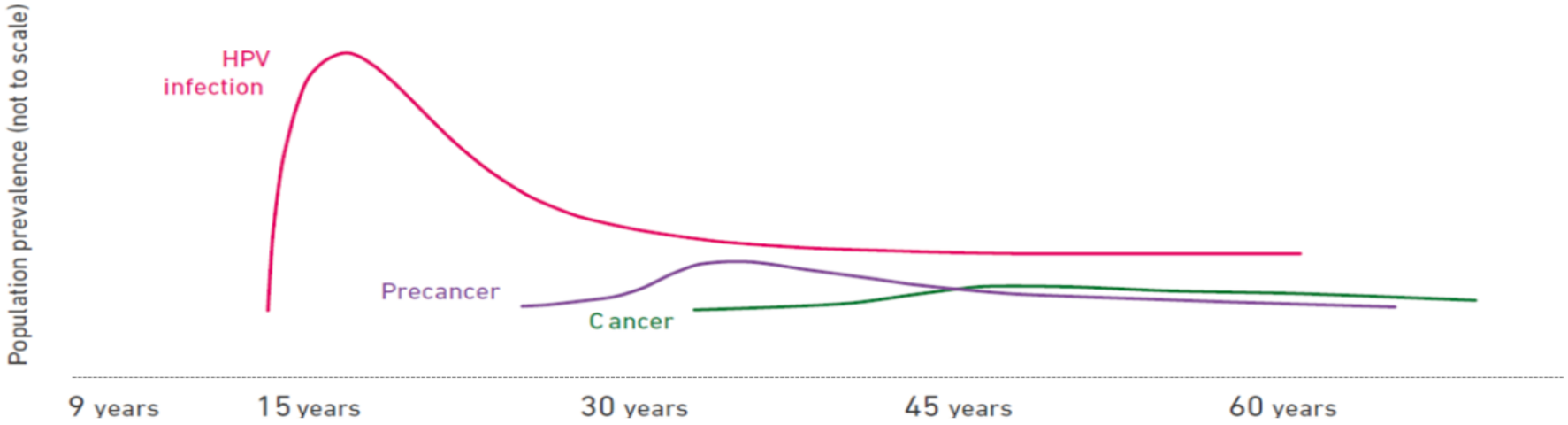
WHO Call for Elimination of Cervical Cancer …. By 2030

MAY 2018: WHO DIRECTOR-GENERAL'S CALL TO ACTION TO ELIMINATE CERVICAL CANCER

World Health Organization
UN WOMEN
unicef
UNFPA
UNAIDS
IAEA International Atomic Energy Agency
International Agency for Research on Cancer
World Health Organization
UNODC United Nations Office on Drugs and Crime
Unitaid Innovation in Global Health
The Global Fund
Gavi The Vaccine Alliance
CLINTON HEALTH ACCESS INITIATIVE
UICC global cancer control
A MEMBERSHIP ORGANISATION FIGHTING CANCER TOGETHER
GHO Global Health Objectives
unfm Université Numérique Francophone Mondiale
NYU Langone Health

World Health Organization

WHO LIFE COURSE APPROACH TO CERVICAL CANCER CONTROL



Primary Prevention

Girls 9-14 years

- HPV vaccination

Girls and boys, as appropriate

- Health information and warnings about tobacco use
- Sexuality education tailored to age & culture
- Condom promotion/provision for those engaged in sexual activity
- Male circumcision

Secondary Prevention

Women > 30 years of age

"Screen and treat" – single visit approach

- Point-of-care rapid HPV testing for high risk HPV types
- Followed by immediate treatment
- On site treatment

Tertiary Prevention and Palliative Care

All women as needed at any age

- Treatment of invasive cancer:
  - Surgery
  - Radiotherapy
  - Chemotherapy
- Palliative care

World Health Organization

CONTINUUM OF CONTROL, ELIMINATION AND ERADICATION

Eradication

Reduction in incidence, prevalence, morbidity or mortality to a locally acceptable level

of disease: incidence reduced to zero in a defined geographical area

of infection: incidence of infection caused by a specific agent reduced to zero.

as a public health problem: achievement of clear and commonly agreed target definitions

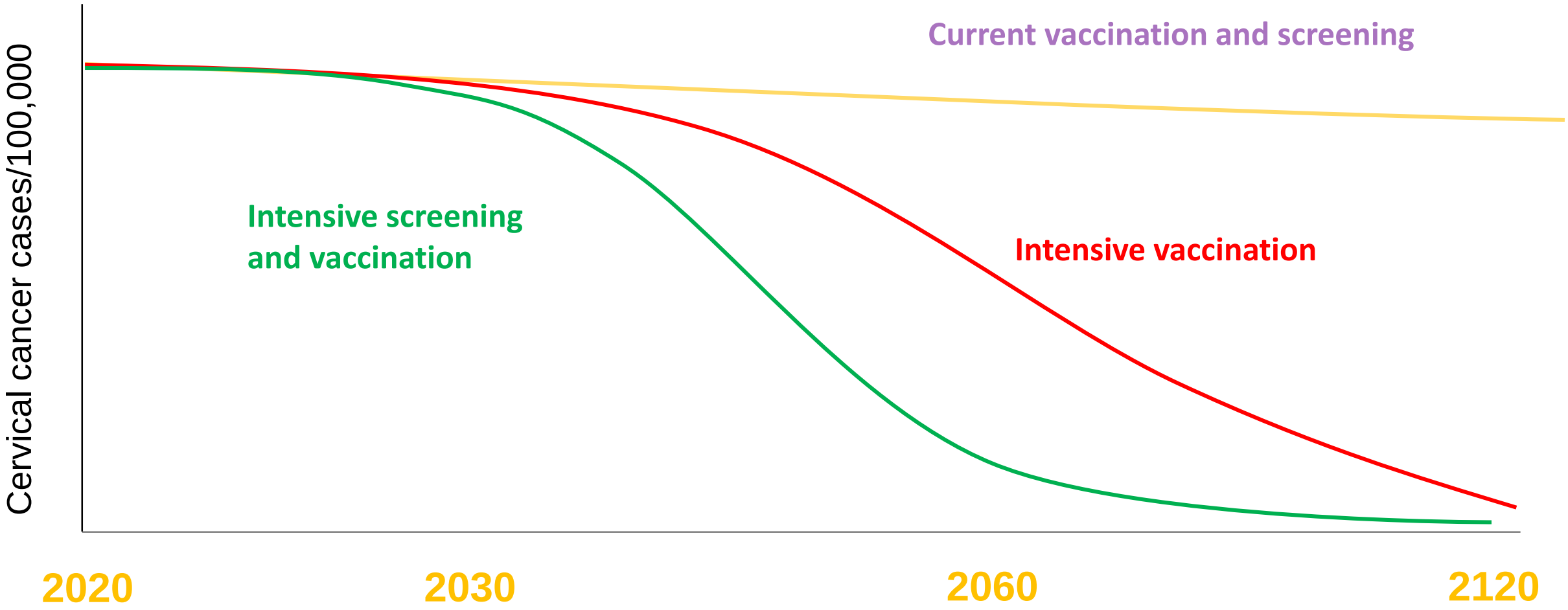
Permanent reduction to zero of the worldwide incidence of infection

Continued intervention measures needed

Intervention measures no longer needed

World Health Organization

CERVICAL CANCER ELIMINATION: CONCEPTUAL FRAMEWORK



World Health Organization

THE ARCHITECTURE TO ELIMINATE CERVICAL CANCER:

VISION: A world without cervical cancer

THRESHOLD: All countries to reach < 4 cases 100,000 women-years

2030 CONTROL TARGETS

90%	70%	90%
of girls fully vaccinated with HPV vaccine by 15 years of age	of women screened with an high precision test at 35 and 45 years of age	of women identified with cervical disease receive treatment and care

SDG 2030: Target 3.4 – 30% reduction in mortality from cervical cancer

The 2030 targets and elimination threshold are subject to revision depending on the outcomes of the modeling and the WHO approval process

World Health Organization

Conclusions

- There is much progress in the cervical cancer space
- New staging system, new information on management strategies, powerful prevention strategies and political will to eliminate this cancer in the foreseeable future
- The time to act is NOW!



END CERVICAL CANCER: PREVENT, TREAT, CARE

Dr. Srabani Mittal

Secretary, AOGIN-India, 2017-19