The role of the pathologist in the diagnosis of gynecological cancer

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Summary

- What is a pathologist ?
- Digital Pathology
- Gynecological cancer
- Conclusions

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The Invisible Doctor

Pathologists have regressed from eminence to anonymity – how did it happen and what should we do about it?

By José I. López

Going back hundreds of years, pathologists, along with psychiatrists, dominated the field of medicine. They were viewed as eminent members of society, even appearing as lead characters in novels of some of the greatest European writers like Thomas Mann or Hermann Hesse.

Modern anatomic pathology was then born in the 19th century in Germany when Rudolf Virchow stated the third principle of cellular theory and contributed to the greatest ever change in the knowledge of human disease processes. His third principle – summarized in the aphorism *omnis cellula e cellula*, meaning that every cell has been originated from the division of another cell – completed the two other basic principles of cellular theory proposed earlier in the century (1839) by Theodor Schwann and Jakob Schleiden.

To consider disease was the result of cell disturbances, and not of humorism, was a giant leap forward at the time, comparable with the discovery of the double helix in 1953 or to the human genome in 2005. Everything changed: biology was reformulated and nothing was the same thereafter. By the dawn of the 20th century, pathologists were at the summit of scientific knowledge. Virchow was the first pathologist nominated for the Nobel Prize of Medicine – in fact he received three nominations – and although he did not take the prize, two histopathologists shared it in 1906: Camillo Golgi and Santiago Ramón y Cajal.

Clinicopathological correlation – a concept defined by Italian Giovanni Battista Morgagni in the 18th century – supported the great advances made in internal medicine in Europe, in particular in France and Great Britain in the early 20th century, when the best clinicians sought the support of pathologists to further their understanding of disease and its clinical relevance to the living patient. The vanguard of pathology then moved from Europe to the USA where it continued its forward trajectory to modernity.

At a Glance

- *Historically, pathologists were viewed as eminent members of society*
- *Since the birth of modern anatomic pathology in the 19th century, pathology has evolved at a dramatic pace; placing it at the center of research and the medical decision-making process*
- *In spite of this, pathologists have become invisible to the public and medical peers*
- *Pathologists are at the forefront of today's most exciting medical advances, and so must take responsibility to reverse this trend, which has caused the future of our field to appear uncertain*

Tarnished by history

Pathology as a medical discipline has evolved tremendously in the last 50 years. Three major milestones have had a dramatic influence: 1) the development of anesthesia – better surgical interventions became possible and surgical pathology was created; 2) the development of the endoscope – a technology that allowed doctors to reach the most recondite sites through natural body openings for study and take small biopsies if needed; 3) the molecular approach – a trend that is very much at the forefront of our evolution right now.

Biopsies and cytologies replaced the autopsy as our main activity, making pathologists integral to the medical decision-making process. And yet, during this dramatic evolution, pathologists have moved to invisibility. Everyone knows what psychiatrists, gynecologists, dermatologists, and so on, do, but very few know anything about pathologists, other than what they see on television.

> *"Europe has a big history in pathology, but this history may somehow be working against us."*

History and tradition are frequently thought necessary for a sustainable evolution but in pathology's case, both have been a heavy backpack that we have had to carry on our climb up the mountain of modernity. Europe has a big history in pathology, but this history may somehow be working against us; it links us unconsciously with forensics and autopsy in the social collective mind. The US don't have this long history of centuries of autopsies behind them and that can be an advantage for American pathologists. But all around the world we have the bad influence of TV – Dr House, Quincy, CSI – in which pathology appears as a simple and easy-reading task under the microscope that almost any doctor can do. Some

students actually tell me the reason that they were attracted to pathology was because of a TV series! What's worse is that we haven't fought against this attitude.

Sadly, this ignorance does not only affect the general public, it applies to those who are an active part of the healthcare system too.

Dispelling myths

Contrary to a belief among our colleagues of other specialties, pathologists do not read the slide under the microscope because nothing is written in cells and tissues. Under the microscope, the pathologist interprets morphological and immunohistochemical data, integrates them with clinical, analytical, molecular and radiological data, and delivers a pathological diagnosis. The pathological diagnosis is much more than a mere result, it's a complex interpretation of multiple and diverse data. Sometimes it is easy, sometimes is not; our job involves seeking out plenty of wolves in sheep's clothing. We need to take responsibility to communicate this message to our medical colleagues.

For the general public, it's important that they know, at the very least, that a pathologist's diagnosis assigns a name to almost every disease, gives crucial information about the extent of the disease, predicts its prognosis, selects the patients that may receive expensive treatments, and evaluates *a posteriori* the effect of these treatments on the patient. How do we do improve

What is a pathologist?

- The pathologist is the medical doctor that makes diagnosis of diseases based on the microscopic examination of tissue samples (biopsies or surgical specimen) or cells (Cytology), and also perform molecular tests in these samples.

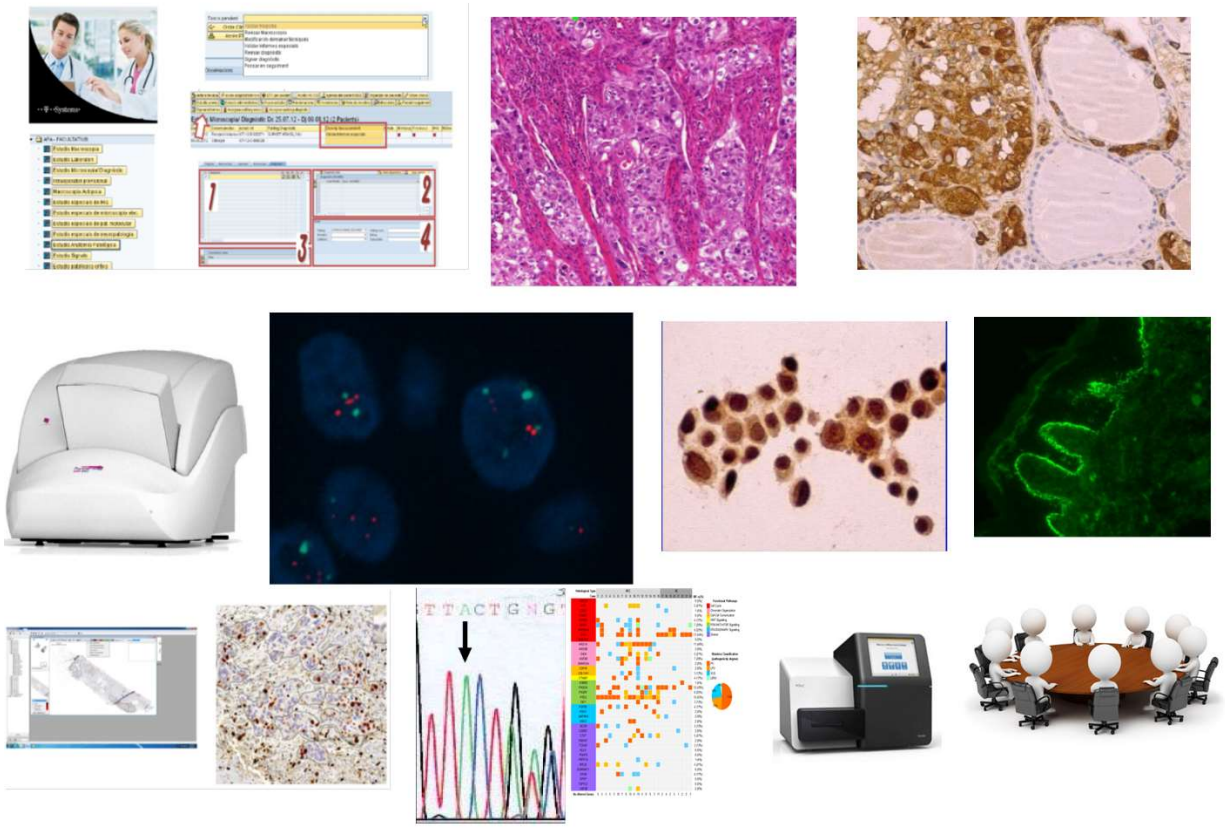
- The patient usually never meet the pathologist, but (particularly in cancer) the pathologist is responsible for the diagnosis of the lesion.

- Technically, a patient do not have cancer until the pathologist make such a diagnosis in a biopsy or a cytology

What is a pathologist?

- The pathologist not only makes the diagnosis of cancer, but also says the type of cancer that the patient has.
- This is very important, because, there are many different types of cancers (some frequent, some rare), and the prognosis depends on the type of tumor
- The patient is always in the center of pathology practice. Pathology starts with the clinical history of the patients, and ends with a pathology report that is sent to the clinician.

What is a pathologist ?



The pathology report contains a diagnosis that is based on microscopic examination and molecular analysis, answering all questions posed by clinician.

Pathology report is standarized following International consensus, like those of the International Collaboration on Cancer Reporting (ICCR)

International Journal of Gynecological Pathology
41:S90–S118, Lippincott Williams & Wilkins, Baltimore

Review Article

Data Set for the Reporting of Endometrial Cancer: Recommendations From the International Collaboration on Cancer Reporting (ICCR)

Xavier Matias-Guiu, M.D., Ph.D., Christina I. Selinger, Ph.D., Lyndal Anderson, F.R.C.P.A., M.Phil., Natalia Buza, M.D., Lora H. Ellenson, M.D., Oluwole Fadare, M.D., Raji Ganesan, M.B.B.S., M.D., F.R.C.Path., Philip P.C. Ip, M.B.Ch.B., F.R.C.Path., Jose Palacios, M.D., Ph.D., Carlos Parra-Herran, M.D., Maria R. Raspollini, M.D., Ph.D., Robert A. Soslow, M.D., Henrica M.J. Werner, M.D., Ph.D., Sigurd F. Lax, M.D., and W. Glenn McCluggage, F.R.C.Path.

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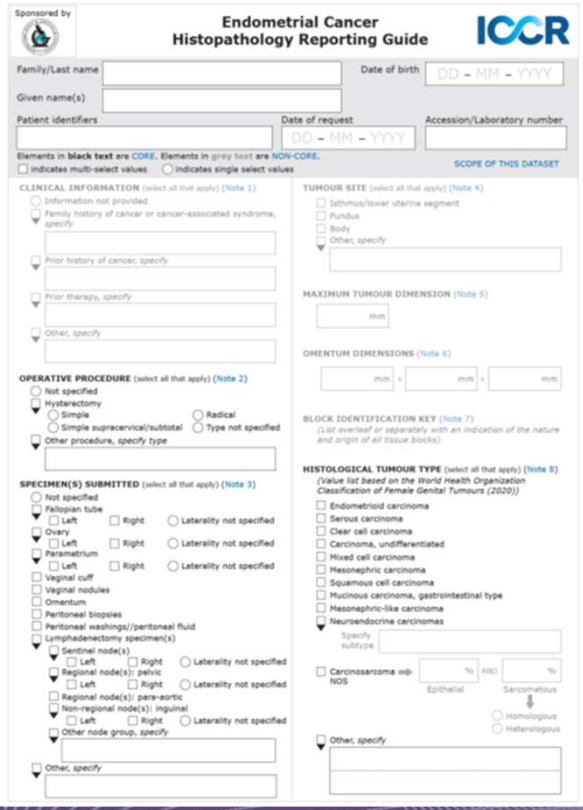

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Endometrial Cancer Histopathology Reporting Guide ICCR

Family/Last name | Date of birth DD – MM – YYYY

Given name(s)

Patient identifiers | Date of request DD – MM – YYYY | Accession/Laboratory number

Elements in **black text** are CORE. Elements in grey text are NON-CORE.
☐ indicates multi-select values ◯ indicates single select values

SCOPE OF THIS DATASET

CLINICAL INFORMATION (select all that apply) (Note 1)
◯ Information not provided
☐ Family history of cancer or cancer-associated syndrome, *specify*
☐ Prior history of cancer, *specify*
☐ Prior therapy, *specify*
☐ Other, *specify*

OPERATIVE PROCEDURE (select all that apply) (Note 2)
◯ Not specified
☐ Hysterectomy
◯ Simple ◯ Radical
◯ Simple supracervical/subtotal ◯ Type not specified
☐ Other procedure, *specify type*

SPECIMEN(S) SUBMITTED (select all that apply) (Note 3)
◯ Not specified
☐ Fallopian tube ☐ Left ☐ Right ◯ Laterality not specified
☐ Ovary ☐ Left ☐ Right ◯ Laterality not specified
☐ Parametrium ☐ Left ☐ Right ◯ Laterality not specified
☐ Vaginal cuff
☐ Vaginal nodules
☐ Omentum
☐ Peritoneal biopsies
☐ Peritoneal washings//peritoneal fluid
☐ Lymphadenectomy specimen(s)
☐ Sentinel node(s) ☐ Left ☐ Right ◯ Laterality not specified
☐ Regional node(s): pelvic ☐ Left ☐ Right ◯ Laterality not specified
☐ Regional node(s): para-aortic
☐ Non-regional node(s): inguinal ☐ Left ☐ Right ◯ Laterality not specified
☐ Other node group, *specify*
☐ Other, *specify*

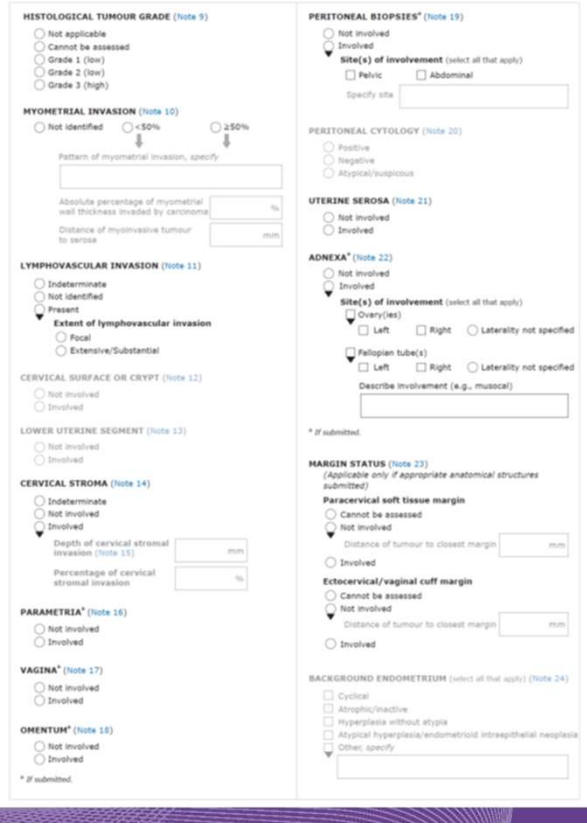
TUMOUR SITE (select all that apply) (Note 4)
☐ Isthmus/lower uterine segment
☐ Fundus
☐ Body
☐ Other, *specify*

MAXIMUM TUMOUR DIMENSION (Note 5)
mm

OMENTUM DIMENSIONS (Note 6)
mm × mm × mm

BLOCK IDENTIFICATION KEY (Note 7)
(List overleaf or separately with an indication of the nature and origin of all tissue blocks)

HISTOLOGICAL TUMOUR TYPE (select all that apply) (Note 8)
(Value list based on the World Health Organization Classification of Female Genital Tumours (2020))
☐ Endometrioid carcinoma
☐ Serous carcinoma
☐ Clear cell carcinoma
☐ Carcinoma, undifferentiated
☐ Mixed cell carcinoma
☐ Mesonephric carcinoma
☐ Squamous cell carcinoma
☐ Mucinous carcinoma, gastrointestinal type
☐ Mesonephric-like carcinoma
☐ Neuroendocrine carcinomas
Specify subtype
☐ Carcinosarcoma *nos* NOS % Epithelial AND % Sarcomatous
◯ Homologous ◯ Heterologous
☐ Other, *specify*



HISTOLOGICAL TUMOUR GRADE (Note 9)
◯ Not applicable
◯ Cannot be assessed
◯ Grade 1 (low)
◯ Grade 2 (low)
◯ Grade 3 (high)

MYOMETRIAL INVASION (Note 10)
◯ Not identified ◯ <50% ◯ ≥50%
Pattern of myometrial invasion, *specify*
Absolute percentage of myometrial wall thickness invaded by carcinoma %
Distance of myoinvasive tumour to serosa mm

LYMPHOVASCULAR INVASION (Note 11)
◯ Indeterminate
◯ Not identified
◯ Present
Extent of lymphovascular invasion
◯ Focal
◯ Extensive/Substantial

CERVICAL SURFACE OR CRYPT (Note 12)
◯ Not involved
◯ Involved

LOWER UTERINE SEGMENT (Note 13)
◯ Not involved
◯ Involved

CERVICAL STROMA (Note 14)
◯ Indeterminate
◯ Not involved
◯ Involved
Depth of cervical stromal invasion (Note 15) mm
Percentage of cervical stromal invasion %

PARAMETRIA* (Note 16)
◯ Not involved
◯ Involved

VAGINA* (Note 17)
◯ Not involved
◯ Involved

OMENTUM* (Note 18)
◯ Not involved
◯ Involved

* *If submitted.*

PERITONEAL BIOPSIES* (Note 19)
◯ Not involved
◯ Involved
Site(s) of involvement (select all that apply)
☐ Pelvic ☐ Abdominal
Specify site

PERITONEAL CYTOLOGY (Note 20)
◯ Positive
◯ Negative
◯ Atypical/suspicious

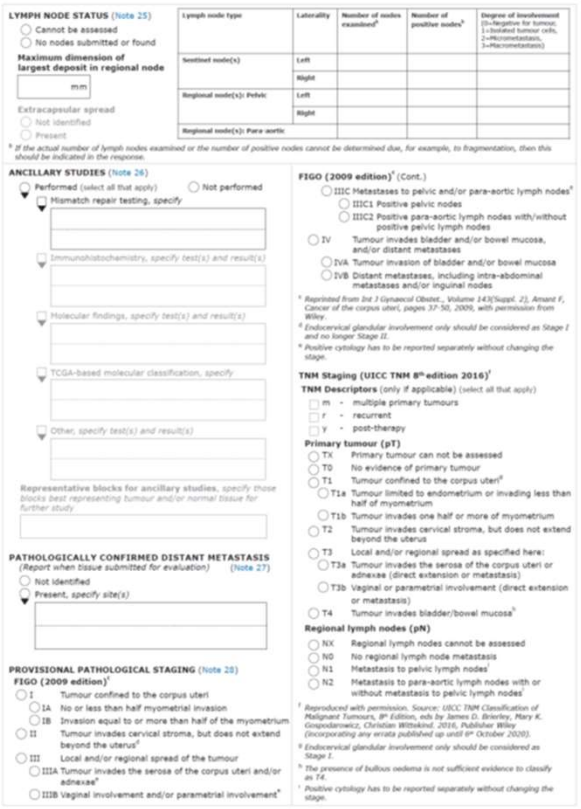
UTERINE SEROSA (Note 21)
◯ Not involved
◯ Involved

ADNEXA* (Note 22)
◯ Not involved
◯ Involved
Site(s) of involvement (select all that apply)
☐ Ovary(ies)
☐ Left ☐ Right ◯ Laterality not specified
☐ Fallopian tube(s)
☐ Left ☐ Right ◯ Laterality not specified
Describe involvement (e.g., musocal)

* *If submitted.*

MARGIN STATUS (Note 23)
(Applicable only if appropriate anatomical structures submitted)
Paracervical soft tissue margin
◯ Cannot be assessed
◯ Not involved
Distance of tumour to closest margin mm
◯ Involved
Ectocervical/vaginal cuff margin
◯ Cannot be assessed
◯ Not involved
Distance of tumour to closest margin mm
◯ Involved

BACKGROUND ENDOMETRIUM (select all that apply) (Note 24)
☐ Cyclical
☐ Atrophic/inactive
☐ Hyperplasia without atypia
☐ Atypical hyperplasia/endometrioid intraepithelial neoplasia
☐ Other, *specify*



LYMPH NODE STATUS (Note 25)
◯ Cannot be assessed
◯ No nodes submitted or found

Lymph node type	Laterality	Number of nodes examined[a]	Number of positive nodes[b]	Degree of involvement (0=Negative for tumour, 1=Isolated tumour cells, 2=Micrometastasis, 3=Macrometastasis)
Sentinel node(s)	Left			
	Right			
Regional node(s): Pelvic	Left			
	Right			
Regional node(s): Para-aortic				

Maximum dimension of largest deposit in regional node mm

Extracapsular spread
◯ Not identified
◯ Present

[a] *If the actual number of lymph nodes examined or the number of positive nodes cannot be determined due, for example, to fragmentation, then this should be indicated in the response.*

ANCILLARY STUDIES (Note 26)
◯ Performed (select all that apply) ◯ Not performed
☐ Mismatch repair testing, *specify*
☐ Immunohistochemistry, *specify test(s) and result(s)*
☐ Molecular findings, *specify test(s) and result(s)*
☐ TCGA-based molecular classification, *specify*
☐ Other, *specify test(s) and result(s)*

Representative blocks for ancillary studies, *specify those blocks best representing tumour and/or normal tissue for further study*

PATHOLOGICALLY CONFIRMED DISTANT METASTASIS
(Report when tissue submitted for evaluation) (Note 27)
◯ Not identified
◯ Present, *specify site(s)*

PROVISIONAL PATHOLOGICAL STAGING (Note 28)
FIGO (2009 edition)[c]
◯ I Tumour confined to the corpus uteri
◯ IA No or less than half myometrial invasion
◯ IB Invasion equal to or more than half of the myometrium
◯ II Tumour invades cervical stroma, but does not extend beyond the uterus[d]
◯ III Local and/or regional spread of the tumour
◯ IIIA Tumour invades the serosa of the corpus uteri and/or adnexae[e]
◯ IIIB Vaginal involvement and/or parametrial involvement[e]
◯ IIIC Metastases to pelvic and/or para-aortic lymph nodes[e]
◯ IIIC1 Positive pelvic nodes
◯ IIIC2 Positive para-aortic lymph nodes with/without positive pelvic lymph nodes
◯ IV Tumour invades bladder and/or bowel mucosa, and/or distant metastases
◯ IVA Tumour invasion of bladder and/or bowel mucosa
◯ IVB Distant metastases, including intra-abdominal metastases and/or inguinal nodes

[c] *Reprinted from Int J Gynaecol Obstet., Volume 143(Suppl. 2), Amant F, Cancer of the corpus uteri, pages 37-50, 2009, with permission from Wiley.*
[d] *Endocervical glandular involvement only should be considered as Stage I and no longer Stage II.*
[e] *Positive cytology has to be reported separately without changing the stage.*

TNM Staging (UICC TNM 8th edition 2016)[f]
TNM Descriptors (only if applicable) (select all that apply)
☐ m - multiple primary tumours
☐ r - recurrent
☐ y - post-therapy

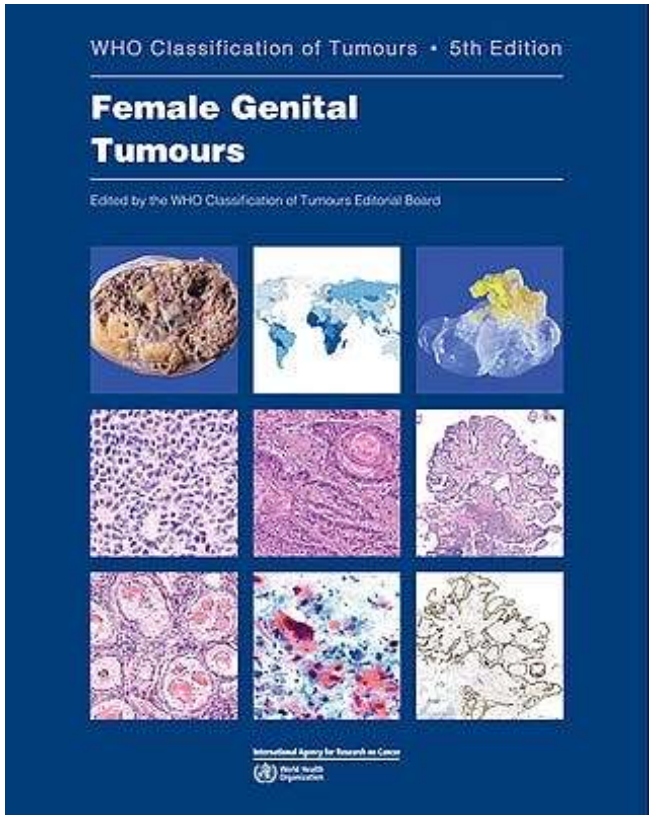
Primary tumour (pT)
◯ TX Primary tumour can not be assessed
◯ T0 No evidence of primary tumour
◯ T1 Tumour confined to the corpus uteri[g]
◯ T1a Tumour limited to endometrium or invading less than half of myometrium
◯ T1b Tumour invades one half or more of myometrium
◯ T2 Tumour invades cervical stroma, but does not extend beyond the uterus
◯ T3 Local and/or regional spread as specified here:
◯ T3a Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)
◯ T3b Vaginal or parametrial involvement (direct extension or metastasis)
◯ T4 Tumour invades bladder/bowel mucosa[h]

Regional lymph nodes (pN)
◯ NX Regional lymph nodes cannot be assessed
◯ N0 No regional lymph node metastasis
◯ N1 Metastasis to pelvic lymph nodes[i]
◯ N2 Metastasis to para-aortic lymph nodes with or without metastasis to pelvic lymph nodes[i]

[f] *Reproduced with permission. Source: UICC TNM Classification of Malignant Tumours, 8th Edition, eds by James D. Brierley, Mary K. Gospodarowicz, Christian Wittekind. 2016, Publisher Wiley (Incorporating any errata published up until 6th October 2020).*
[g] *Endocervical glandular involvement only should be considered as Stage I.*
[h] *The presence of bullous oedema is not sufficient evidence to classify as T4.*
[i] *Positive cytology has to be reported separately without changing the stage.*

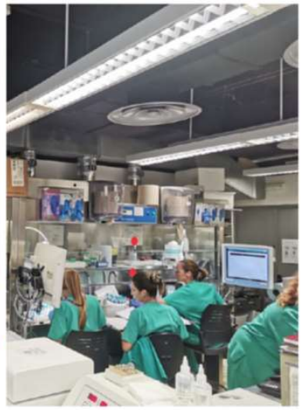
Matias-Guiu X at al: Data set for reporting of Endometrial Cancer: Recommendations from International Collaboration on Cancer Reporting (Int J Gynecol Pathol 2022)

WHO, Female Genital Tumors, 2020



In the multidisciplinary tumor board (MTB), all Medical specialist (surgeons, medical oncologists, radiation oncologists, radiologists, nurses, and pathologists, discuss the best clinical management of the patient. The role of the pathologist is crucial in MTB.

- Tissue handling is an important task.
- Tissues have to be managed in an appropiate way to allow pathologic and molecular results.
- Pathologist is not the only person important in this. Time between tumor resection at the operating room and reception in pathology department is important.



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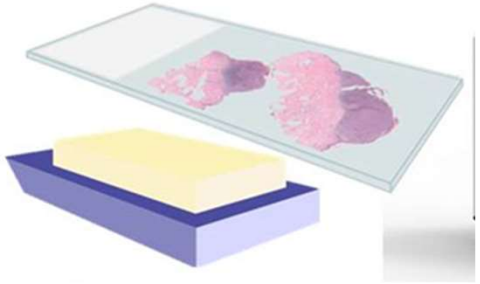
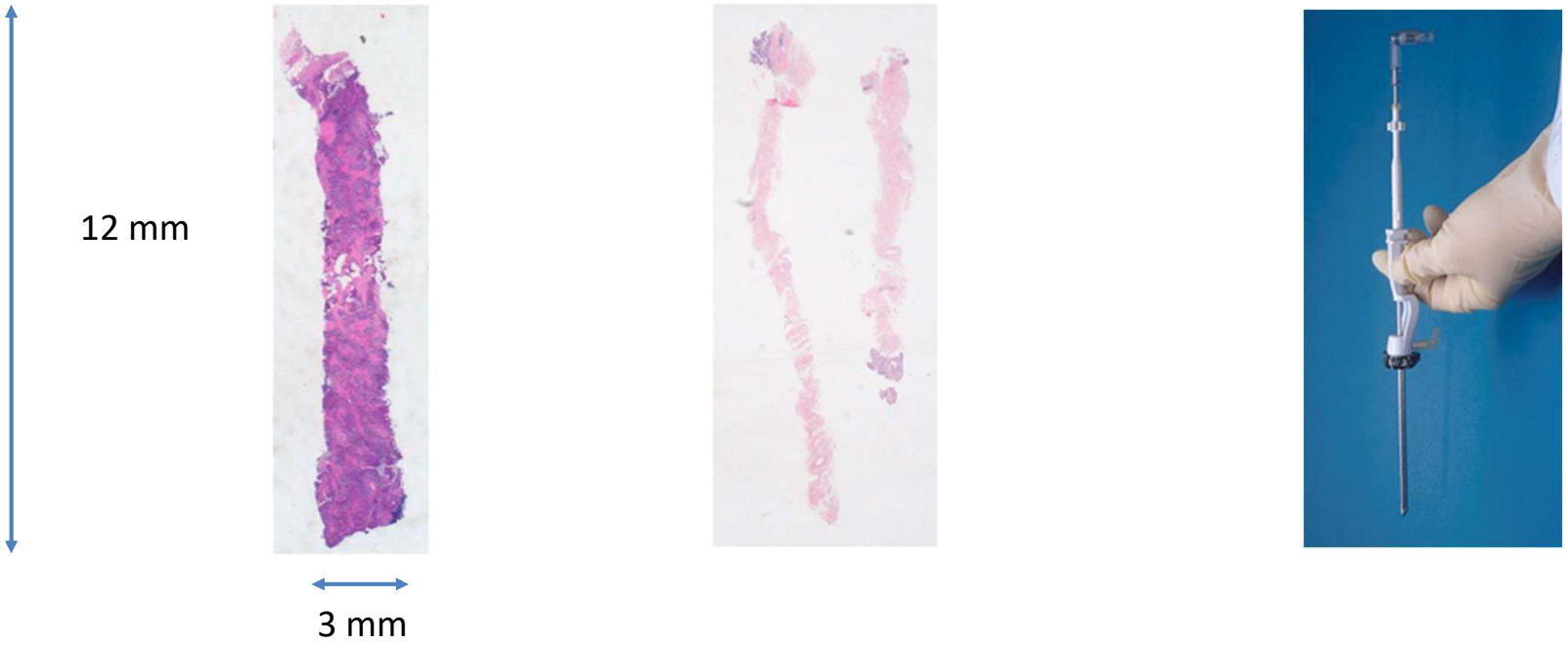


- The amount of tumor tissue in the biopsy is also important.



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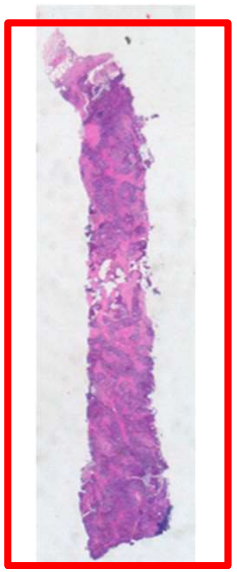
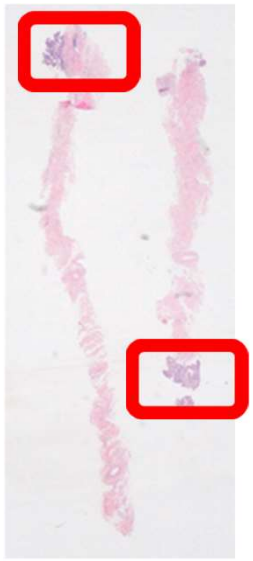
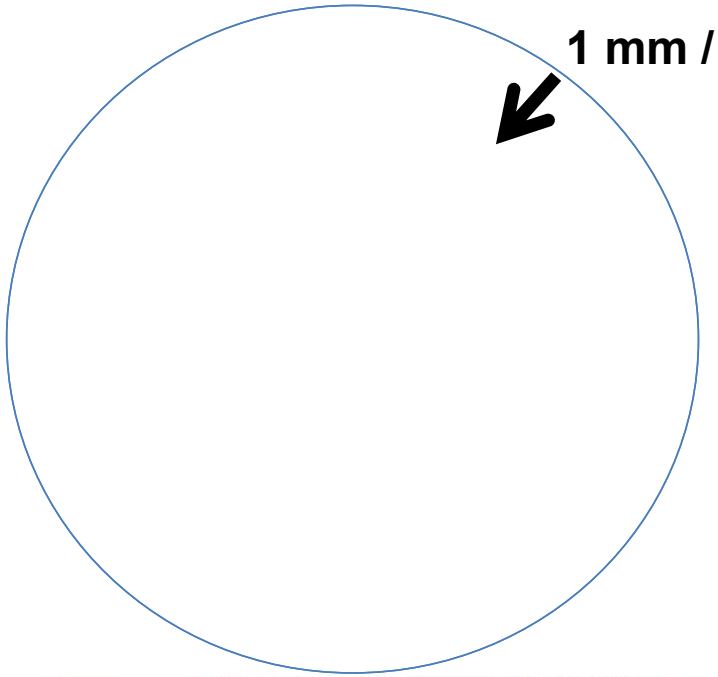




Preanalytics and Precision Pathology

Pathology Practices to Ensure Molecular Integrity of Cancer Patient Biospecimens for Precision Medicine

Carolyn C. Compton, MD, PhD; James A. Robb, MD; Matthew W. Anderson, MD, PhD; Anna B. Berry, MD; George G. Birdsong, MD; Kenneth J. Bloom, MD; Philip A. Branton, MD; Jessica W. Crothers, MD; Allison M. Cushman-Vokoun, MD, PhD; David G. Hicks, MD; Joseph D. Khoury, MD; Jordan Laser, MD; Carrie B. Marshall, MD; Michael J. Misialek, MD; Kristen E. Natale, DO; Jan Anthony Nowak, MD, PhD; Damon Olson, MD; John D. Pfeifer, MD, PhD; Andrew Schade, MD; Gail H. Vance, MD; Eric E. Walk, MD; Sophia Louise Yohe, MD



- Delayed fixation
- Overfixation

- Cellularity
- Necrosis
- Inflammatory component
- Tumor heterogeneity
- Changes after neoadjuvant therapy

- We use the microscope
- Microscopical image allow us to see if there is cancer or not
- Moreover, we say the type of cancer that the patient has
- Diagnosis of cancer is not always easy

All these people are genetically different, but we can identify them just with a quick look.....

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..... But some of them may be quite similar

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..... Some tumors have a microscopical imatge that can be misleading

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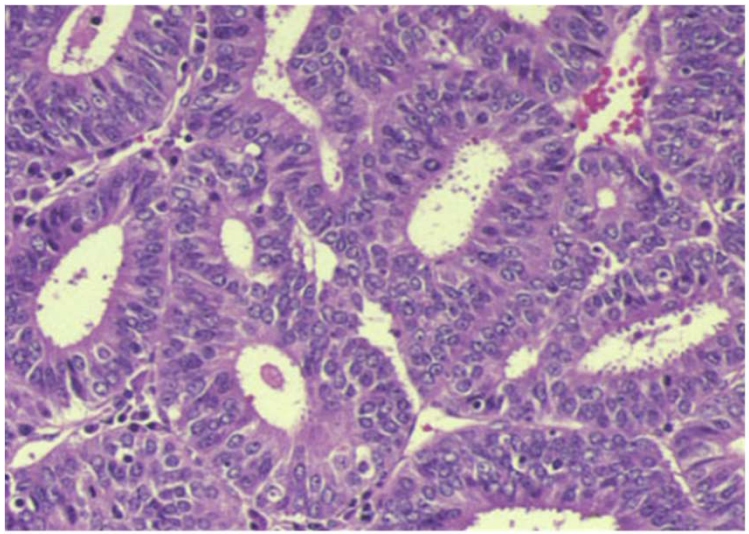
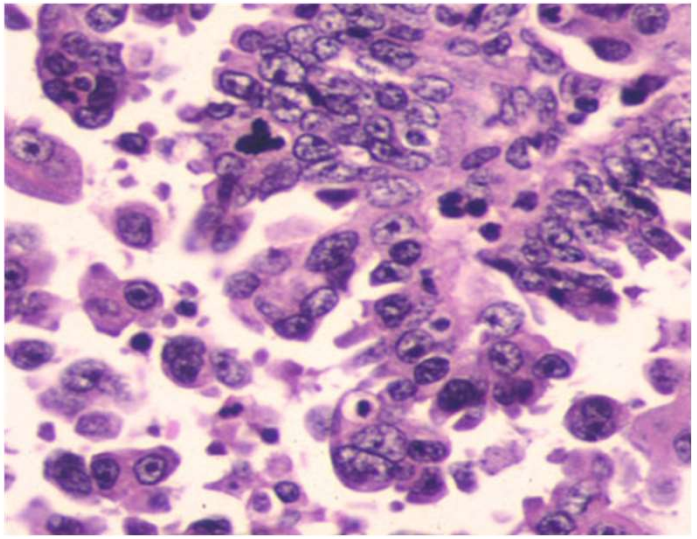
Tumors from the same organ may have very diferent prognosis or evan surgical approach, Endometrial cancer

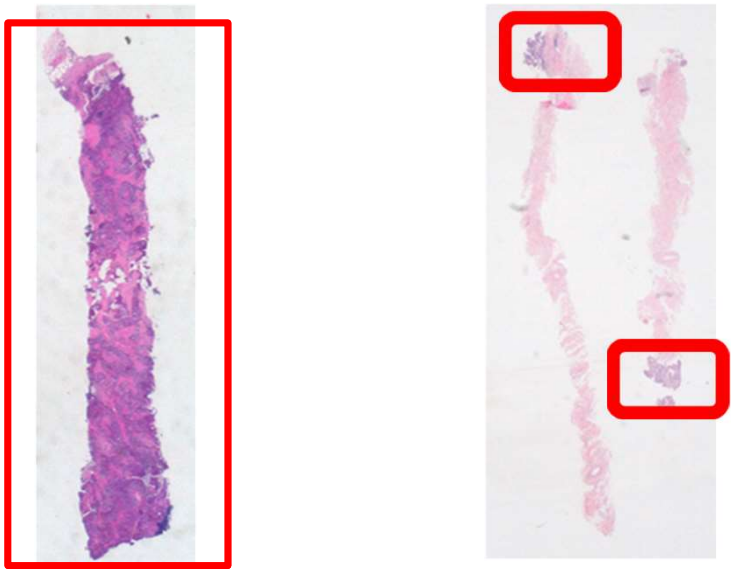


Low grade endometrioid



Serous

Diagnosing a tumor in a small biopsy can be tricky if the most informative area is not contained in the biopsy



Diagnosing a tumor in a small biopsy can be tricky if the most informative area is not contained in the biopsy

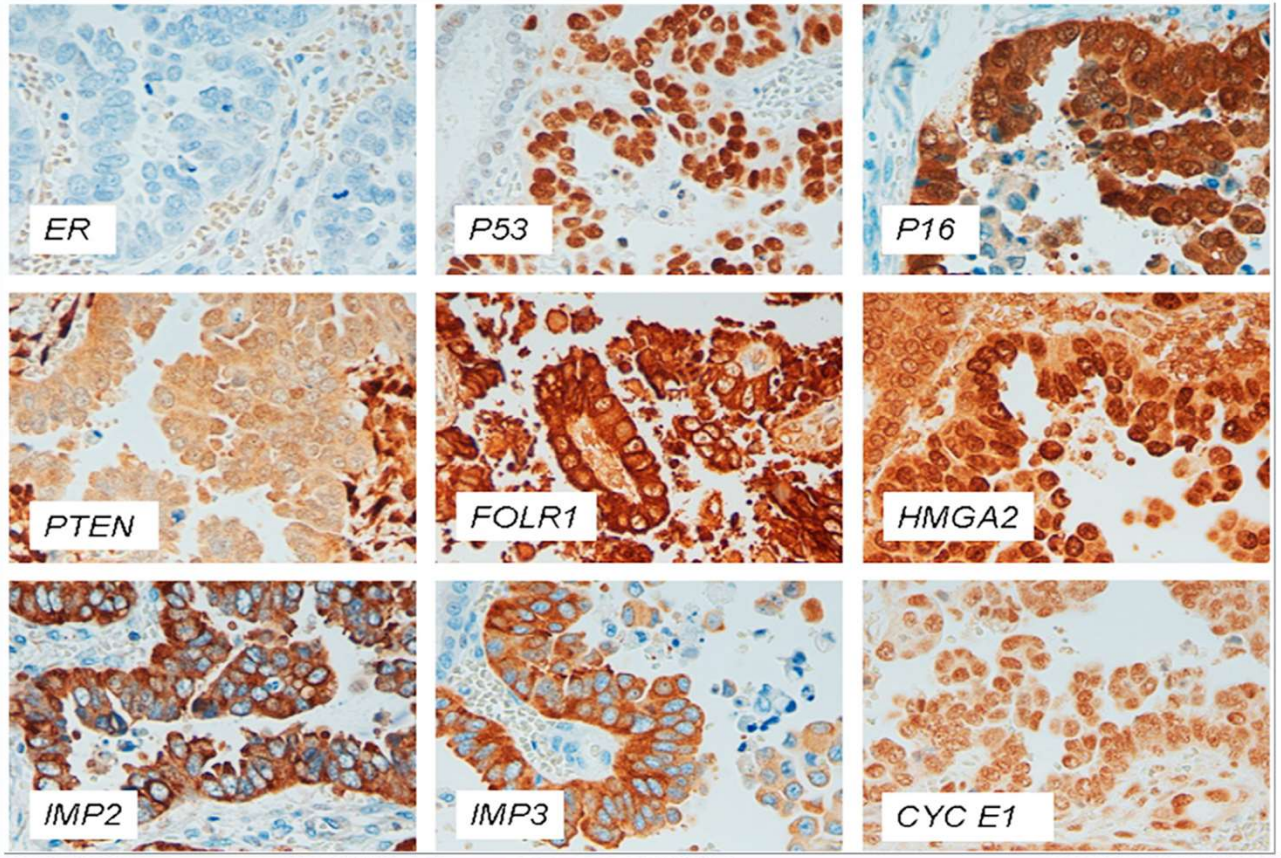
Diagnosing a tumor in a small biopst can be tricky if the most informative area is not contained in the biopsy

When the micoscopic imatge is not very informative, we have to use other techniques....

..... by they require time, and sometimes more tumor tissue.

- Detection of Proteins / Immunohistochemistry
- Detection od DNA or RNA sequences (Molecular Pathology)

Immunohistochemistry allows detection of proteins in tissue, and it is very important in diagnosis



From single cell approaches to next generation sequencing

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PCR/qPCR	Sanger Sequencing	Comprehensive Panels	Whole-Exome Sequencing
eg, EGFR, ALK, BRAF		*eg, TMB*	
Measures binary expression in small number of genes[1,2]		Quantifies complex cancer mutation landscape[4-7]	
Roche, QIAGEN	GENEWIZ	CARIS, FOUNDATIONONE	ThermoFisher SCIENTIFIC, illumina
• Sequence information on a small number of recurrent mutations[3]	• Highly accurate sequencing reads up to 1000 basepairs per run for up to 96 DNA templates[5]	• Predefined set of genes (typically 170-500 genes)[8,9]	• All coding regions (180,000 exons), making up ~1% of genome[10] • 85% of mutations contributing to disease are found in the coding region[11]

Genetic readout

- Some of these proteins or DNA/RNA alterations are called “Biomarkers”

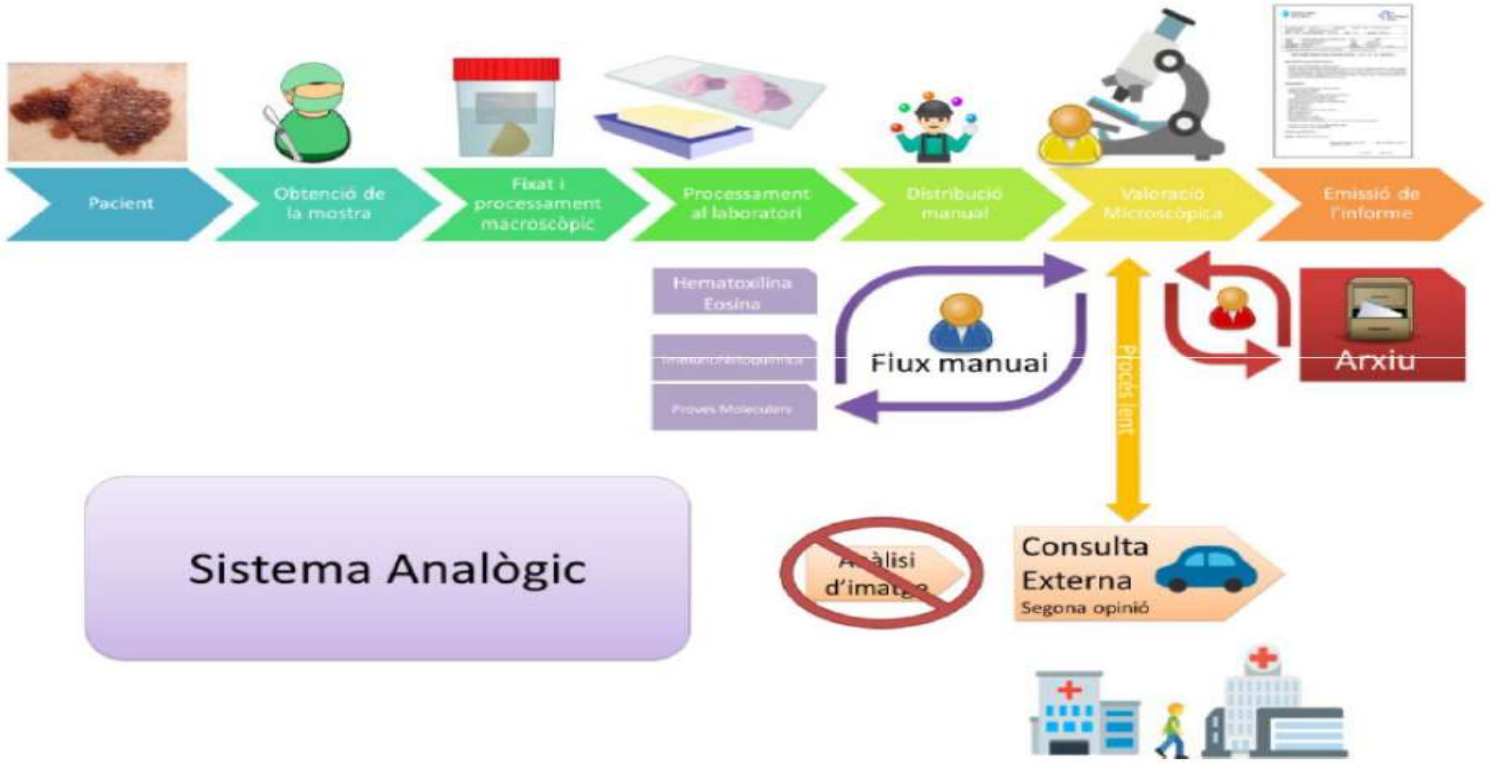
- Biomarkers allow distinction of different types of tumor, but also help in taking the appropriate treatment.

- There is no “perfect” biomarker.

- Quality control is very important to assure that every laboratory is performing the tests appropriatelly.

Summary

- What is a pathologist ?
- Digital Pathology
- Gynecological cancer
- Conclusions


Pacient
Obtenció de la mostra
Fixat i processament macroscòpic
Processament al laboratori
Distribució manual
Valoració Microscòpica
Emissió de l'informe
Hematoxilina Eosina
Flux manual
Arxiu
Procés ient
Sistema Analògic
Consulta Externa
Segona opinió

Transportation of biologic material between hospitals

Problems in diagnostic reproducibility. Lack of uniformity in reporting

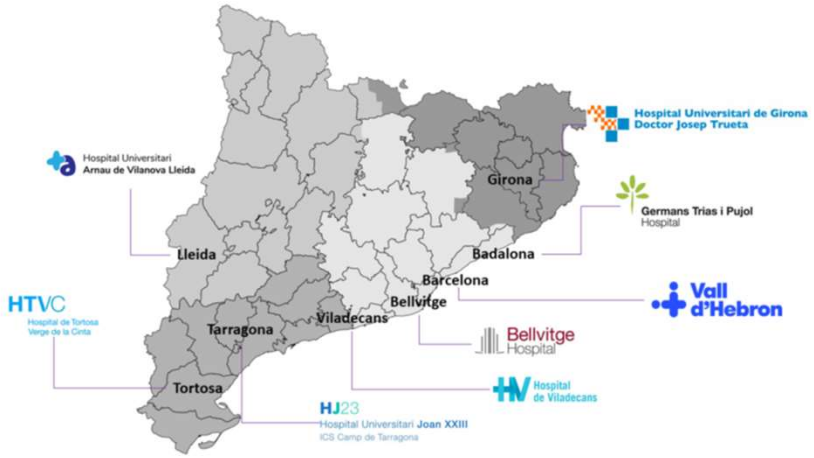
Impossibility of having experts in very specific areas in all centers

Lack of optimal interaction between Pathology Departments and Other facilities

Patients interchange between centers

Problems in objective assessment of some biomarkers

1- Innovació organitzativa:



diagnostics

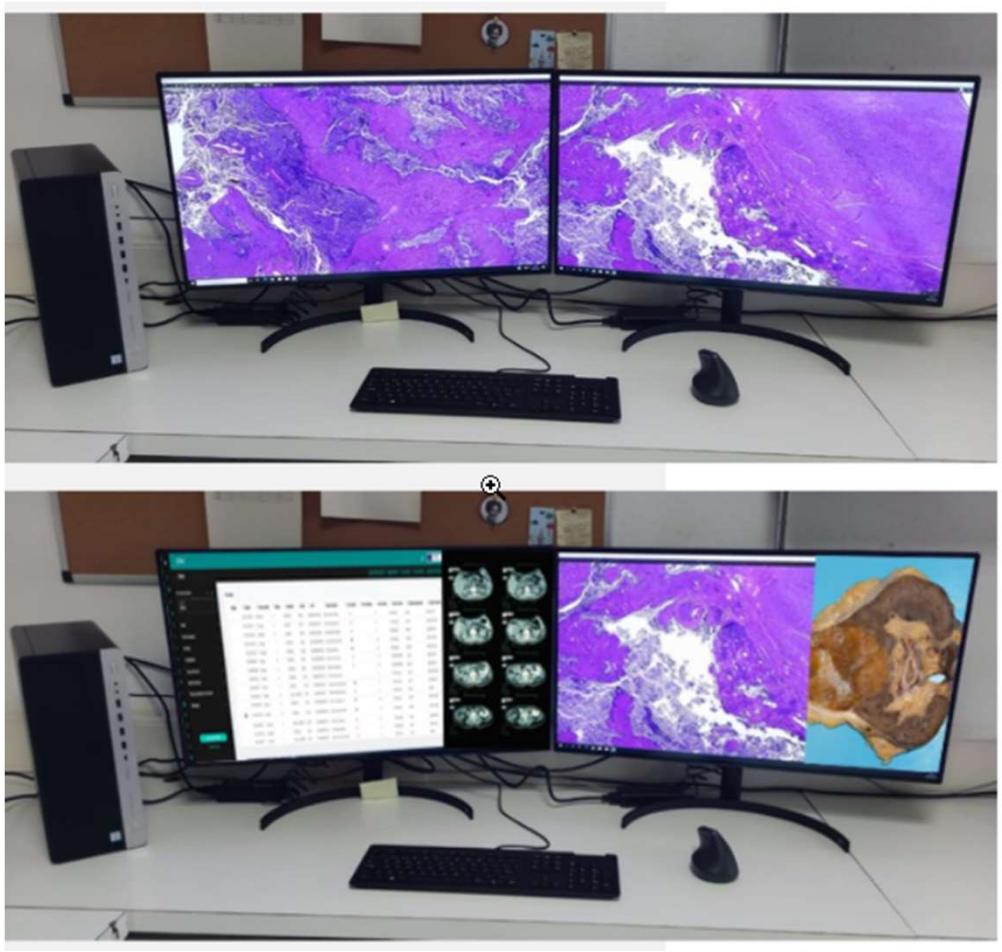
MDPI

Article

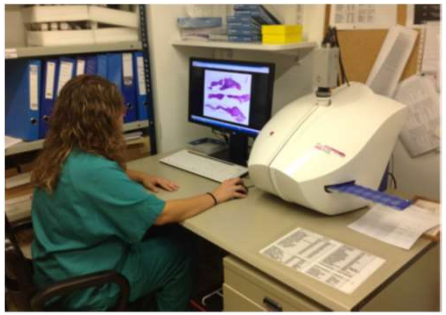
DigiPatICS: Digital Pathology Transformation of the Catalan Health Institute Network of 8 Hospitals—Planification, Implementation, and Preliminary Results

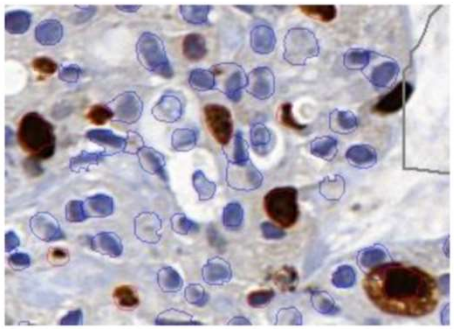
Jordi Temprana-Salvador [1,*], Pablo López-García [2], Josep Castellví Vives [1], Lluís de Haro [2], Eudald Ballesta [2], Matias Rojas Abusleme [3], Miquel Arrufat [4], Ferran Marques [5], Josep R. Casas [5], Carlos Gallego [6], Laura Pons [7], José Luis Mate [7], Pedro Luis Fernández [7], Eugeni López-Bonet [8], Ramon Bosch [9], Salomé Martínez [10], Santiago Ramón y Cajal [1,†] and Xavier Matias-Guiu [11,12,†]

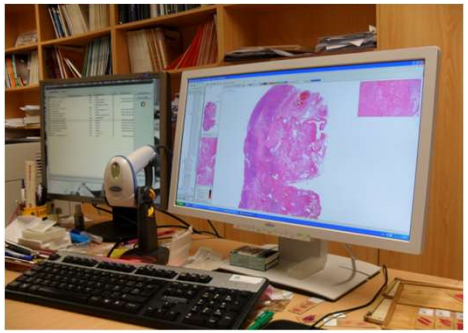
Workstation- Viewer

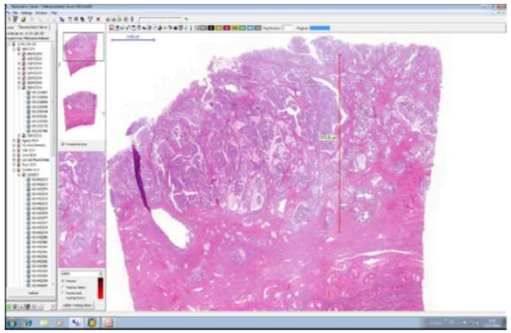


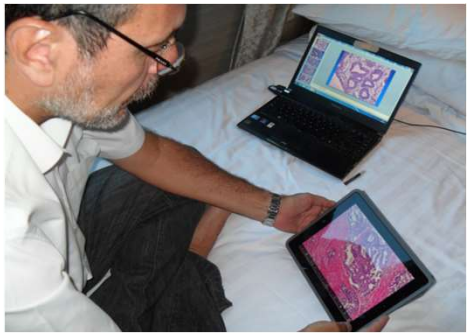
Digital pathology is an opportunity





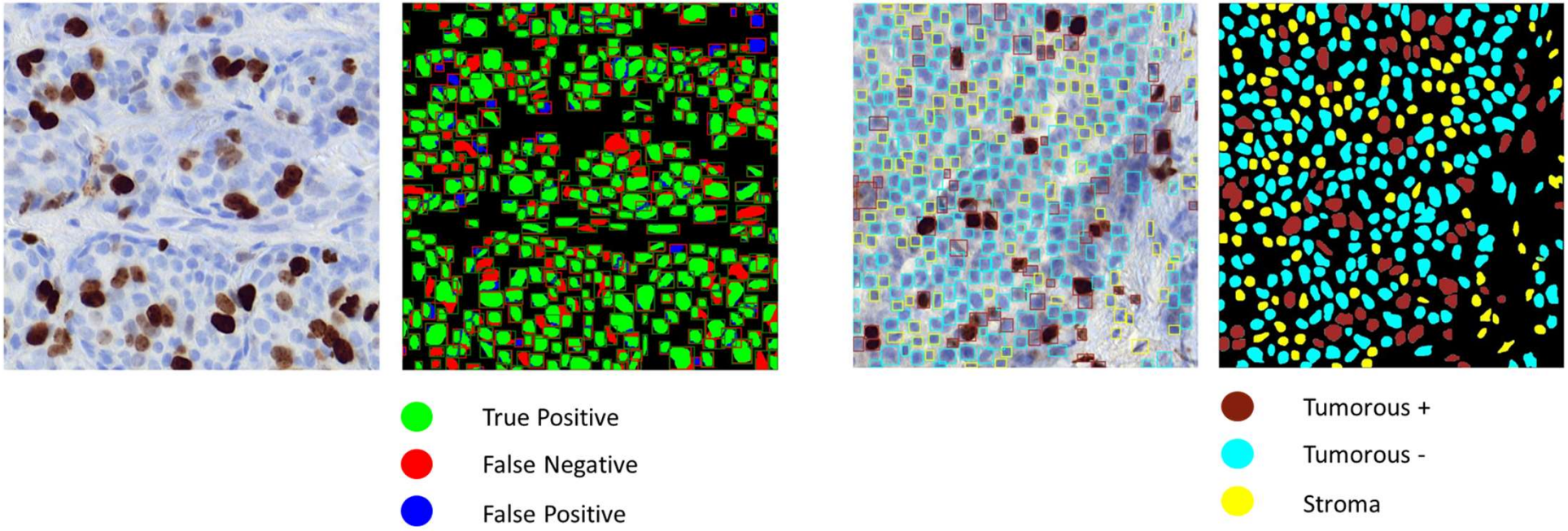






Ki-67 Biomarker

- Cell detection -> Cells classification



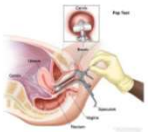
Identifying abnormal cells in cervical smears from patients with endometrial carcinoma

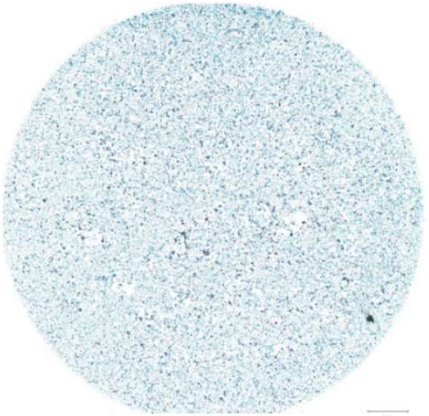
Sensitivity of Cervico-vaginal Cytology in Endometrial Carcinoma: A Systematic Review and Meta-analysis

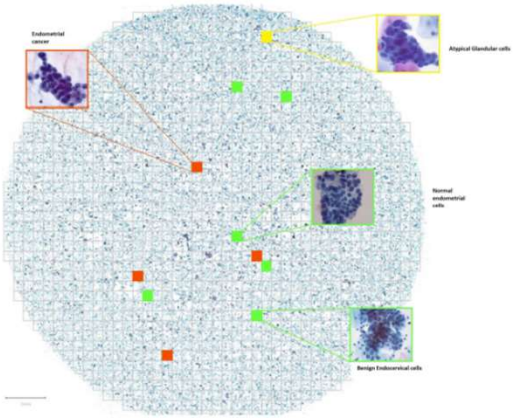
Jon Frias-Gomez, MStat[1,2]; Yolanda Benavente, MStat[1,3]; Jordi Ponce, MD, PhD[4]; Joan Brunet, MD, PhD[5,6,7]; Raquel Ibáñez, PhD[1]; Paula Peremiquel-Trillas, MD, MPH[1,2]; Nuria Baixeras, MD[8]; Alba Zanca, TECHN[8]; Josep Maria Piulats, MD, PhD[6,9]; Álvaro Aytés, PhD[10]; Xavier Matias-Guiu, MD, PhD[6,9]; Francesc Xavier Bosch, MD, PhD[1]; Silvia de Sanjosé, MD, PhD[3,11]; Laia Alemany, MD, PhD[1,3]; and Laura Costas, MD, PhD[1]; on behalf of the Screenwide Team

A Simple Cervicovaginal Epigenetic Test for Screening and Rapid Triage of Women With Suspected Endometrial Cancer: Validation in Several Cohort and Case/Control Sets

Chiara Herzog, PhD[1,2]; Fátima Marín, PhD[1,3]; Allison Jones, BSc[1]; Iona Evans, PhD[1]; Daniel Reisel, PhD[1]; Elisa Redl, MSc[1,2]; Lena Schreiberhuber, MSc[1,2]; Sonia Payubi, PhD[1]; Beatriz Pelegrina, MSc[4]; Álvaro Carmona, PhD[4]; Paula Peremiquel-Trillas, MD[4]; Jon Frias-Gomez, MSc[4]; Marta Pineda, PhD[5,6]; Joan Brunet, MD, PhD[5,6,7]; Jordi Ponce, PhD[5,6]; Xavier Matias-Guiu, PhD[5,6]; Silvia de Sanjosé, PhD[3,11]; Laia Alemany, PhD[1,11]; Adeola Olaitan, MD[12]; Michael Wong, PhD[12]; Davor Jurkovic, PhD[12]; Emma J. Crosbie, MD[13,14]; Adam N. Rosenthal, PhD[1]; Line Bjørge, PhD[15,16]; Michal Zikan, PhD[17]; Lukas Dostalek, MD, PhD[18]; David Cibula, PhD[18]; Karin Sundström, PhD[19]; Joakim Dillner, PhD[19]; Laura Costas PhD[1,11]; and Martin Widschwendter, MD[1,8,9,20]







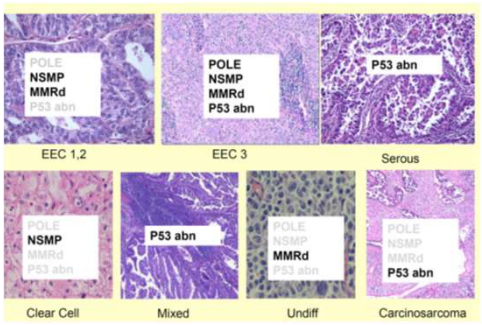
Distinguishing molecular subtypes of endometrial carcinoma by AI

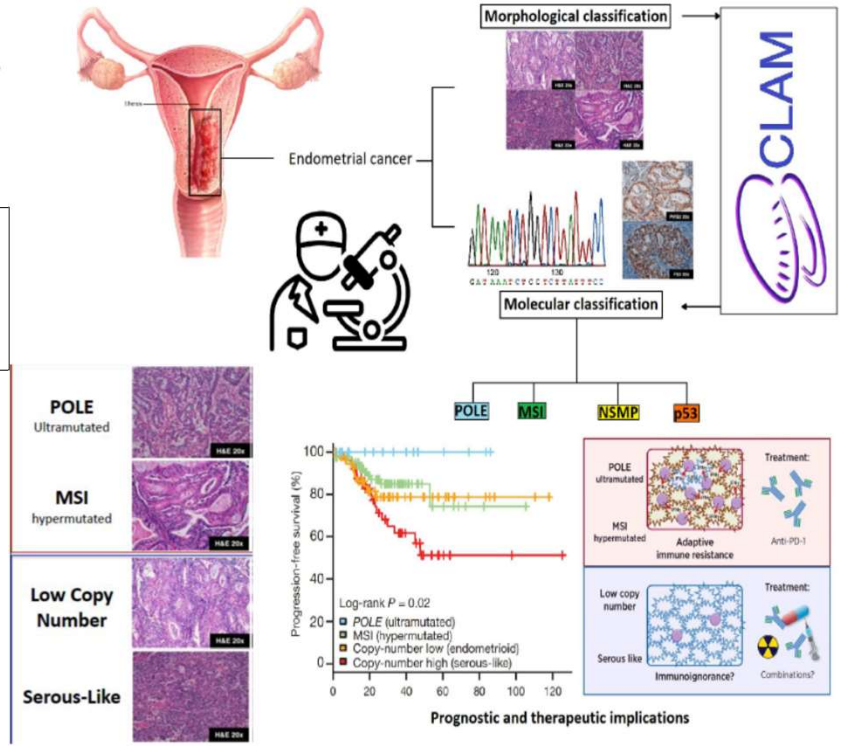
Predicting endometrial cancer subtypes and molecular features from histopathology images using multi-resolution deep learning models

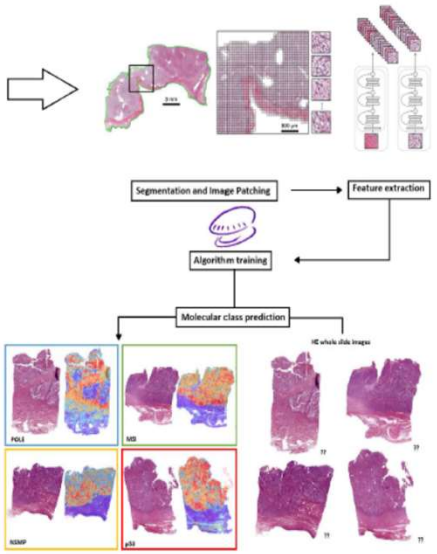
Runyu Hong,[1,2] Wenke Liu,[1,2] Deborah DeLair,[3] Narges Razavian,[4,5] and David Fenyö[1,2,6,*]

Problems

- **Influence of preanalytics (specimen vs aspirates)**
- **Influence of morphology, since molecular subtypes are not equally distributed among histologic types**







Summary

- What is a pathologist ?
- Digital Pathology
- Gynecological cancer
- Conclusions

Ovarian Cancer

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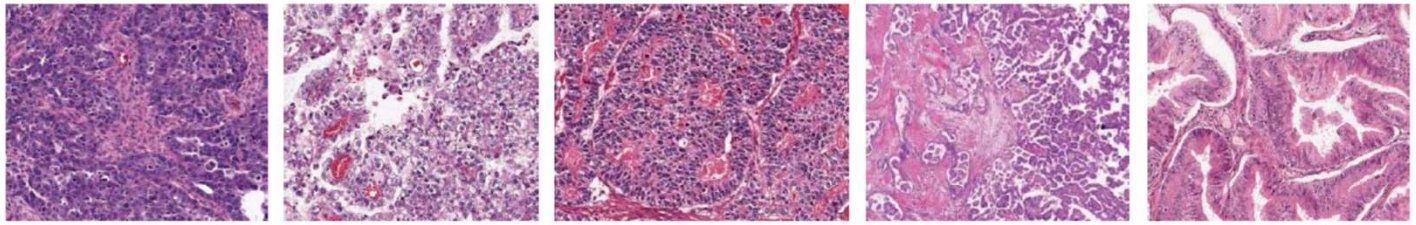
There are five main subtypes of epithelial ovarian carcinoma (EOC) – each with different clinicopathological features

There is frequent advanced presentation with loco-regional dissemination in the peritoneal cavity
High-grade serous carcinomas are the most common type of OC[1]

70%	10%	10%	5%	3%
High-grade serous carcinoma	Clear cell carcinoma	Endometrioid carcinoma	Low-grade serous carcinoma	Mucinous carcinoma



Most common → Least common

Percentage of subtypes of epithelial ovarian cancer taken from: Hollis R and Gourley C. *Cancer Biol Med.* 2016; 13(2): 236-247
Images adapted from: Conklin C & Gilks CB. *Exp Rev Obst Gyn.* 2013;8:1–16
EOC=Epithelial ovarian carcinoma; OC=Ovarian cancer
1. Conklin C & Gilks CB. *Exp Rev Obst Gyn.* 2013;8:1–16; 2. Hollis R and Gourley C. *Cancer Biol Med.* 2016; 13(2): 236-247

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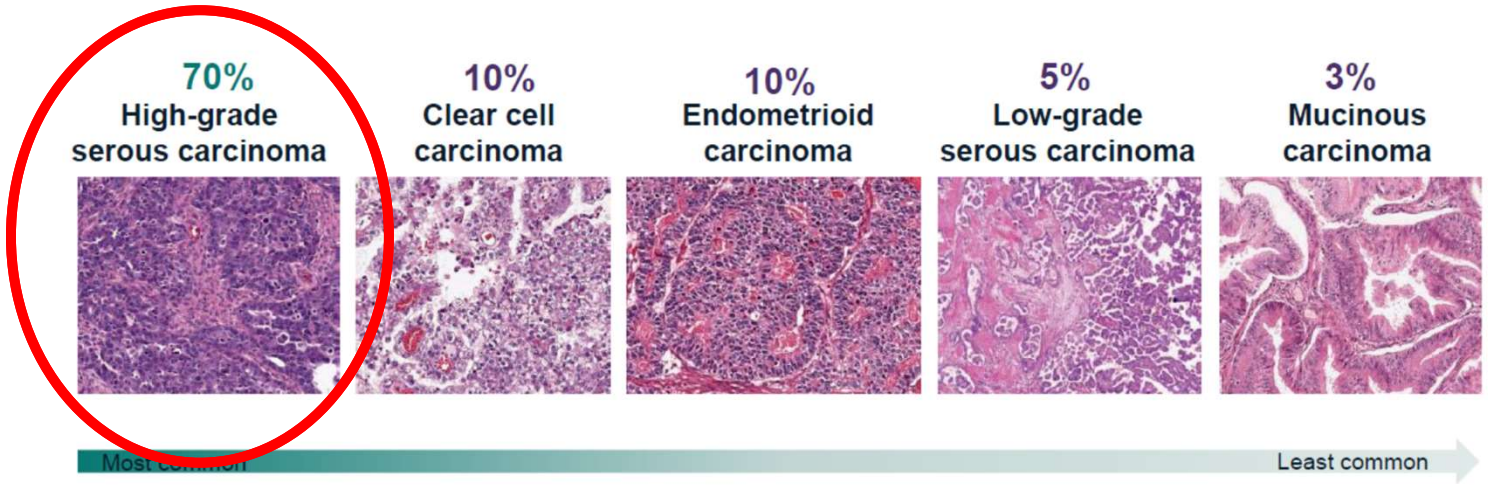

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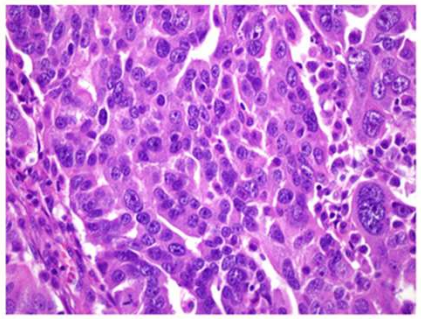
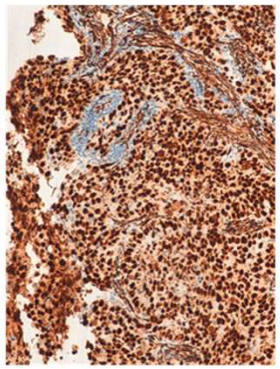
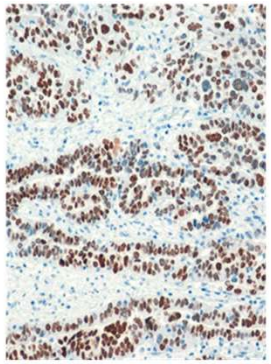
ENGOT
European Network of Gynaecological Oncological Trial groups

High grade serous carcinoma

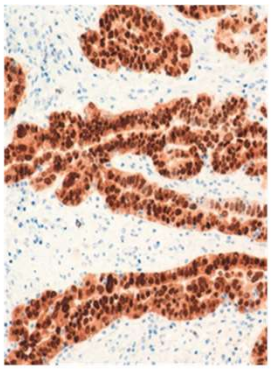




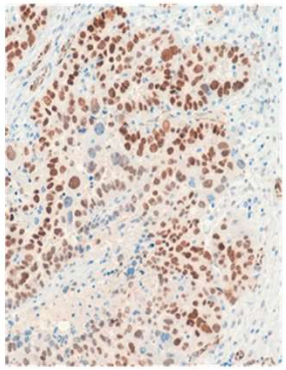
WT-1



p53

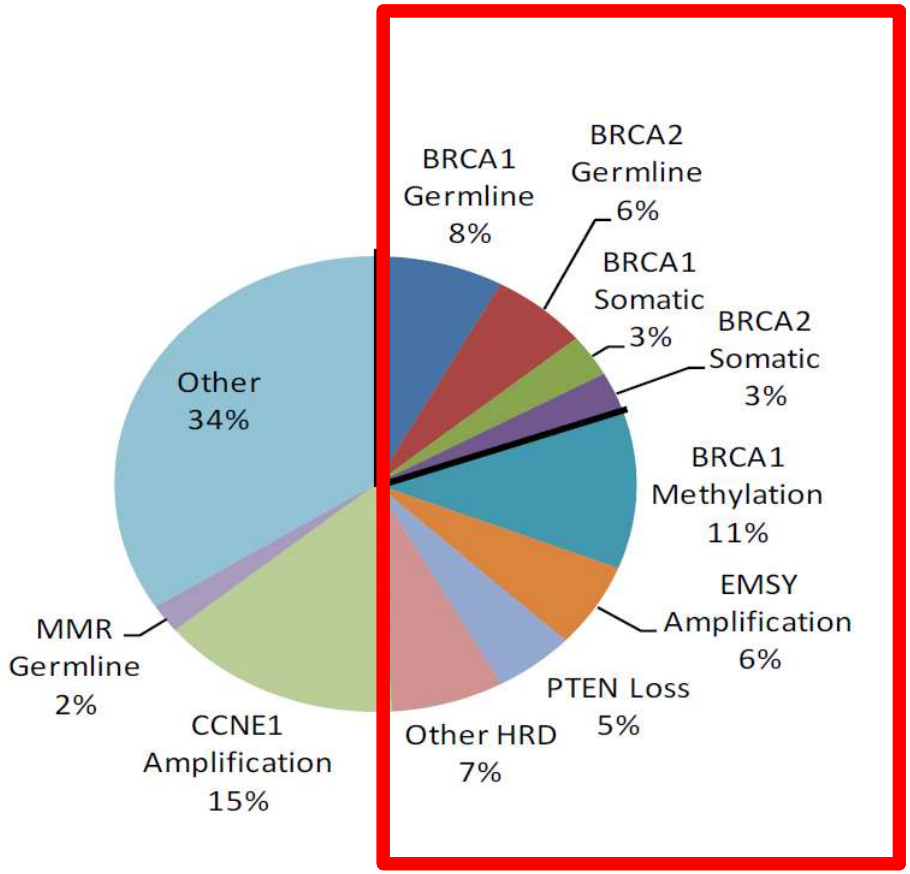


PAX 8



ER

Perspectiva histórica



Around 50% of high grade serous carcinomas show HRD, Homologous recombination deficiency

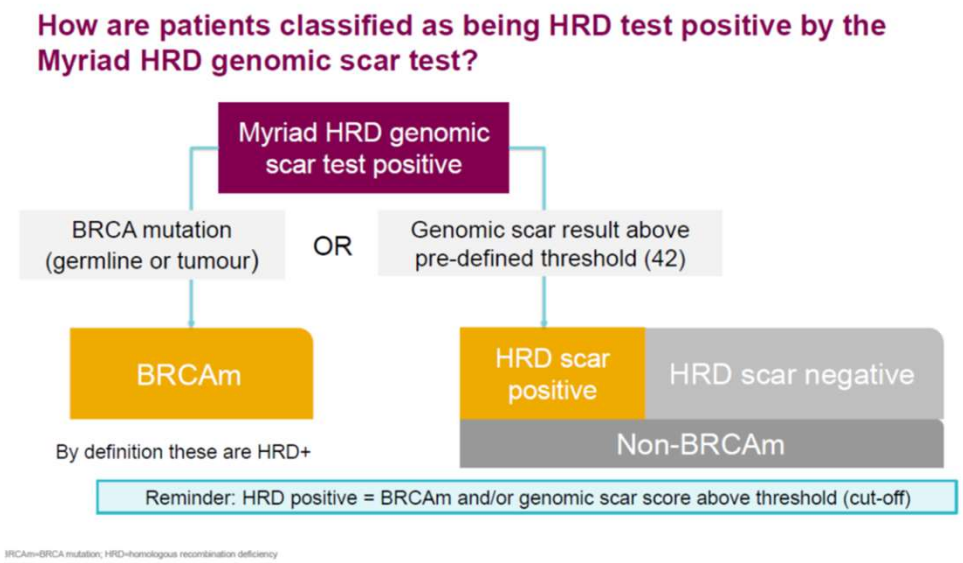
Testing HRD in tumor tissue to predict response to Chemotherapy and PARP inhibition

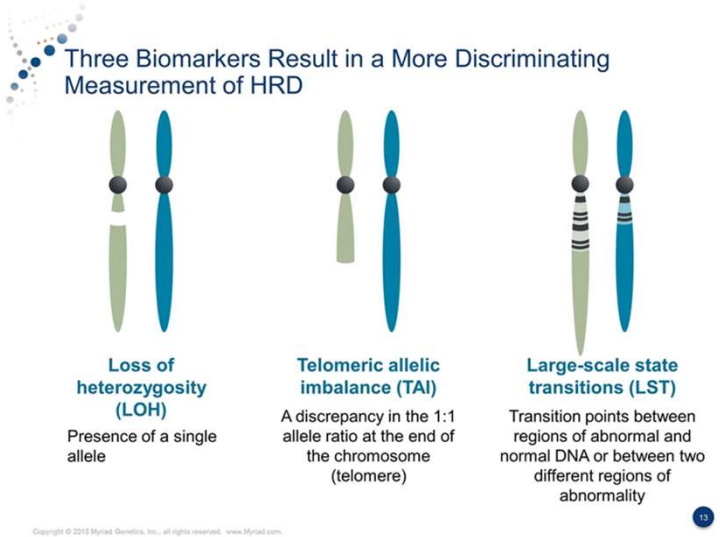
The Cancer Genome Atlas Research Network. Integrated Genomic Analyses of Ovarian Carcinoma. *Nature.* 2011;474(7353): 609–615

HRD (Homologous recombination deficiency)

- Homologous recombination is a mechanism that allows normal cell to repair some DNA lesions
- 50% of ovarian high grade serous carcinomas have Homologous recombination deficiency (HRD)
- Tumors with HRD have better prognosis, and respond better to platinum-based therapies and PARP inhibition

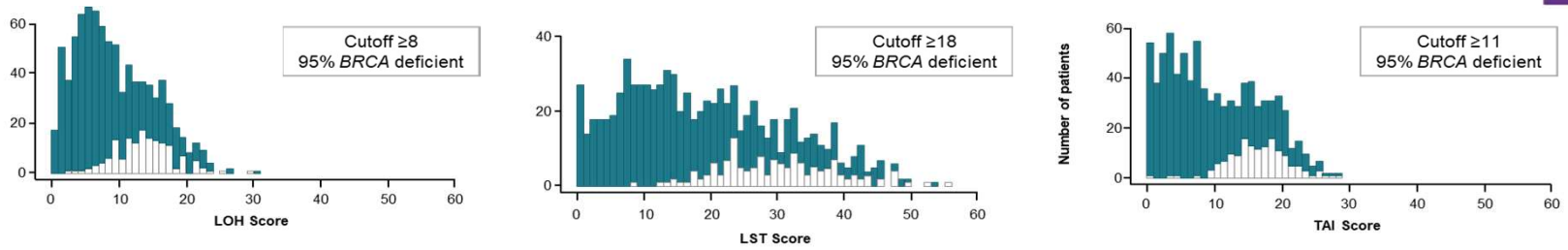
Myriad my Choice CDx plus

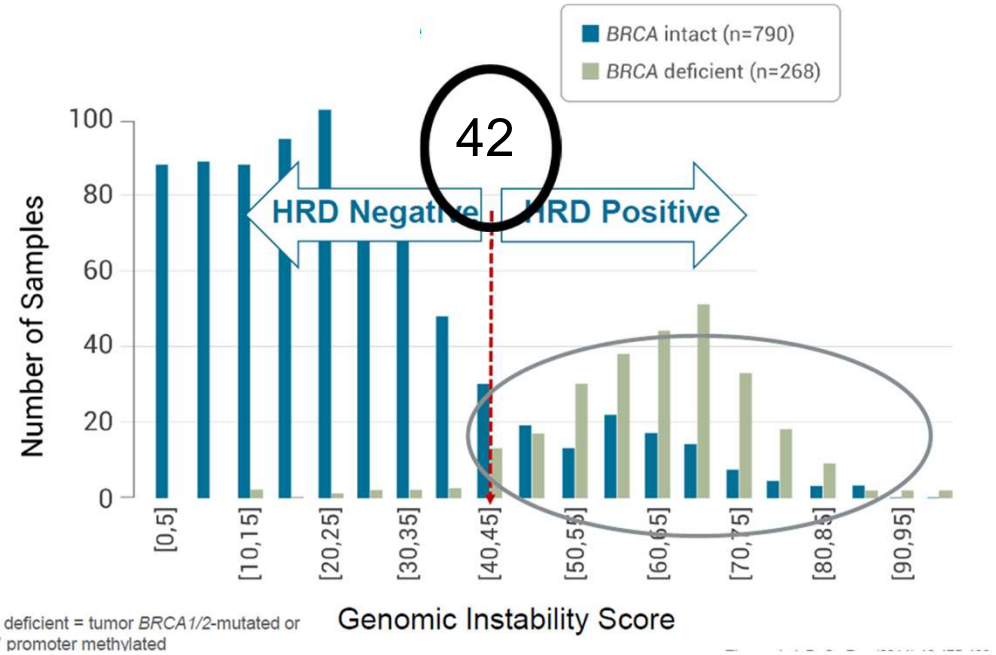




Myriad Genetic Laboratories. Myriad myChoice CDx. Disponible en: https://myriad-oncology.com/mychoice-cdx/ (ultimo acceso: Mayo 2021)

Myriad my Choice CDx plus





1.Timms KM, Abkevich V, Hughes E, Neff C, Reid J, Morris B, et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. *Breast Cancer Res*. 2014;16:475. 2. Hennessy BT, Timms KM, Carey MS, Gutin A, Meyer LA, Flake DD, 2nd, et al. Somatic mutations in BRCA1 and BRCA2 could expand the number of patients that benefit from poly (ADP ribose) polymerase inhibitors in ovarian cancer. *J Clin Oncol*. 2010;28:3570-6. 3.The Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011;474:609-15. 4.The Cancer Genome Atlas Research NetworkComprehensive molecular portraits of human breast tumours. *Nature*. 2012;490:61-70.

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A range of commercial HRD genomic instability kits and locally developed academic tests are now available

Commercial tests

Assay[a]	TS0500 HRD[1]	HRD focus[1]	HRD solution[2]	QIAseq HRD panel[3]
Instrument	Illumina NextSeq 500/550, NovaSeq	Illumina NextSeq 500/550, NovaSeq 6000	Illumina NextSeq 500/550, NovaSeq	Compatible with all major NGS platforms[b]

LDTs

Assay[a]	NOGGO-GIS assay[4]	Geneva HRD test[5]	CytoSNP[6]	Leuven HRD test[7]	RAD51 foci[8]	sWGS[9]
Instrument	Illumina sequencer	Affymetrix GeneChip	Illumina Infinium CytoSNP-850K BeadChip microarray	Illumina NovaSeq	RAD51 foci assay	Illumina or BGI DNBseq platforms

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

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SPECIAL ARTICLE

ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer

R. E. Miller[1,2], A. Leary[3], C. L. Scott[4,5], V. Serra[6], C. J. Lord[7,8], D. Bowtell[4,5], D. K. Chang[9,10], D. W. Garsed[4,5], J. Jonkers[11], J. A. Ledermann[12], S. Nik-Zainal[13,14], I. Ray-Coquard[15,16], S. P. Shah[17], X. Matias-Guiu[18], E. M. Swisher[19] & L. R. Yates[20,21]*

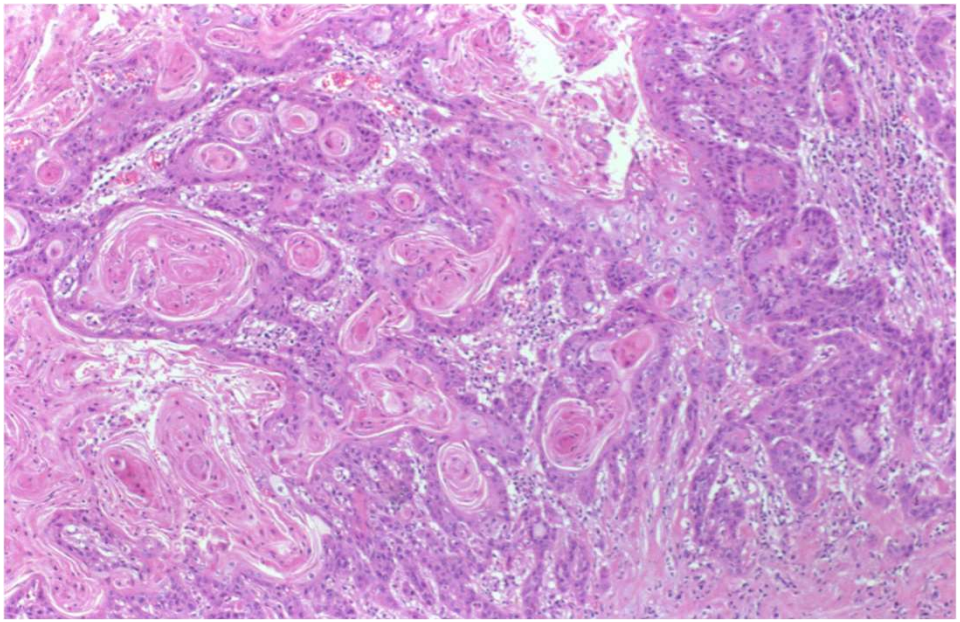
Consensus recommendation

Pathological evaluation of the tumour tissue specimens used for assessment of somatic molecular alterations is essential. It is recommended that a pathologist with experience in gynaecological pathology should be a member of the team and responsible for confirming diagnosis, assessing sample adequacy, selection of tumour area, and quantification of tumour cells, inflammatory cells and necrosis. An integrated pathology-molecular report is highly recommended.

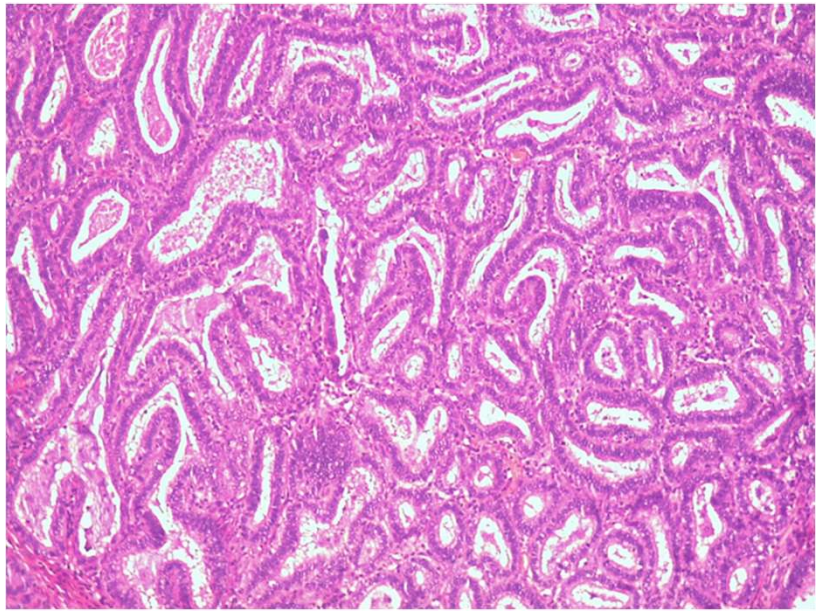
(Level of agreement = 100%; total agreement)

Cervical Cancer

Squamous cell carcinoma



Adenocarcinoma



- Squamous Cell carcinoma, HPV-associated
- Squamous cell carcinoma, HPV-independent
- Squamous cell carcinoma, NOS

- Adenocarcinoma in situ, HPV-associated
- Adenocarcinoma, HPV-associated
- Adenocarcinoma in situ, HPV-independent
- Adenocarcinoma, HPV-independent, gastric type
- Adenocarcinoma, HPV-independent, clear cell type
- Adenocarcinoma, HPV-independent, mesonephric type
- Other adenocarcinomas

FDA approves pembrolizumab for advanced cervical cancer with disease progression during or after chemotherapy

On June 12, 2018, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck and Co. Inc.) for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.

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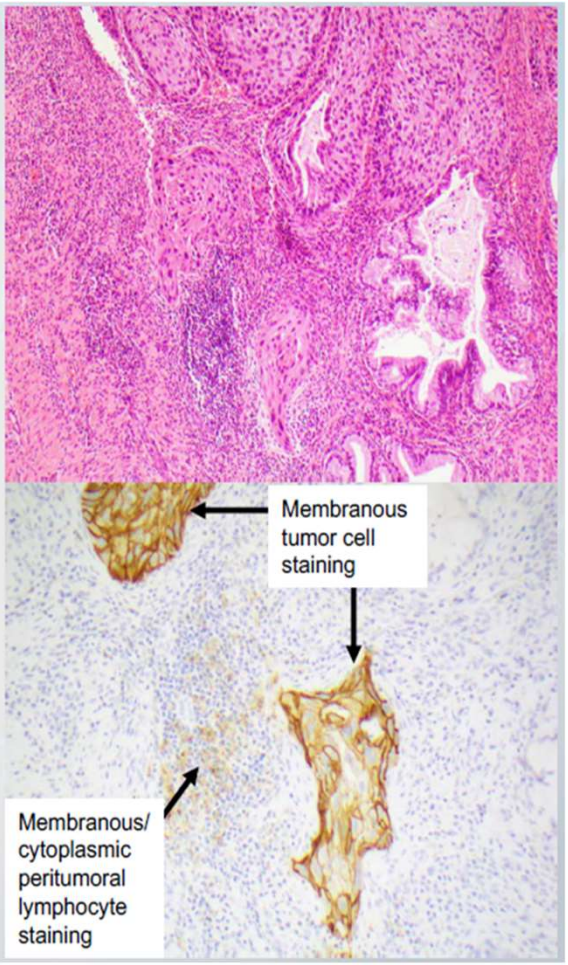
European Commission Approves Merck's KEYTRUDA® (pembrolizumab) Plus Chemotherapy, With or Without Bevacizumab, for Patients With Persistent, Recurrent or Metastatic Cervical Cancer Whose Tumors Express PD-L1 (CPS≥1)

4/29/2022

Approval Based on Overall Survival Benefit Demonstrated in Phase 3 KEYNOTE-826 Trial

How to Assess the CPS:

- Any CPS from 1-100 is positive.
  - 100 is the maximum allowable score.
- CPS is averaged across the entire tumor.
  - Don't just count the hot spots!
- CPS should be assessed at 20x to ensure that even focal positivity is captured.
- Tumor cell staining must be membranous.
- Immune cell staining may be membranous or cytoplasmic.
- PD-L1+ lymphocytes and macrophages must be associated with response to the tumor.
  - Location can be either intratumoral or peritumoral.
  - Lymphoid aggregates count, provided they are within or immediately adjacent to the tumor.



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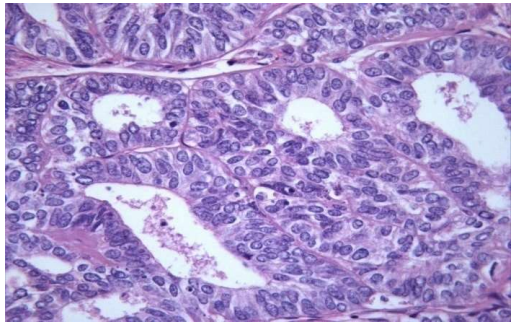
PDL-1

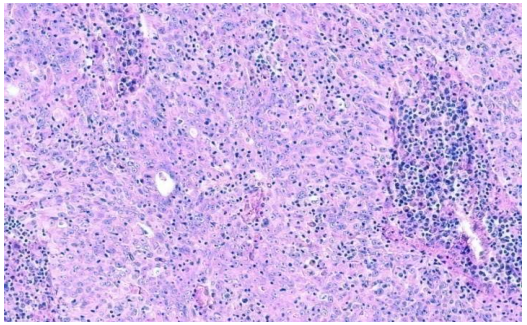
Mills A, USCAP 2019

Endometrial Cancer

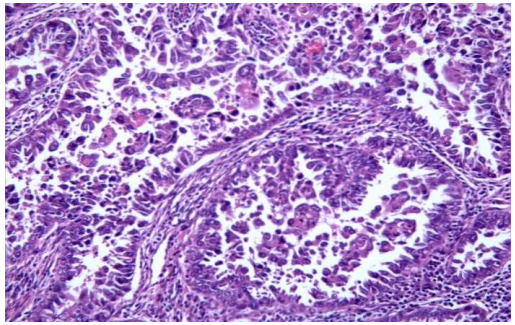
HISTOLOGIC TYPES OF ENDOMETRIAL CARCINOMA



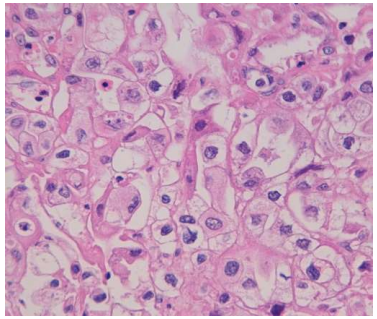
EEC 1,2



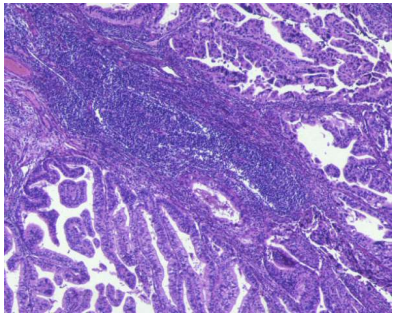
EEC 3



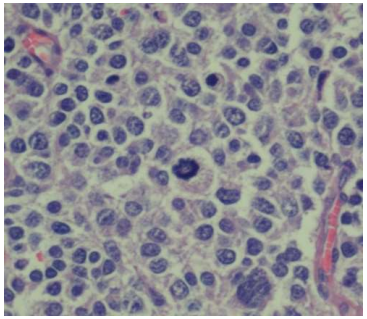
Serous



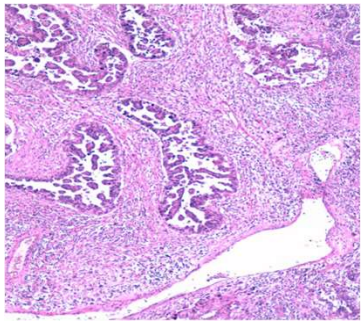
Clear Cell



Mixed



Undiff



Carcinosarcoma

PROGNOSTIC/PREDICTIVE

TCGA-based surrogate

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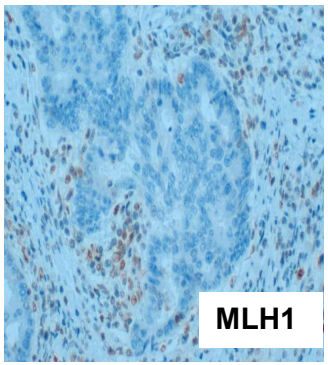
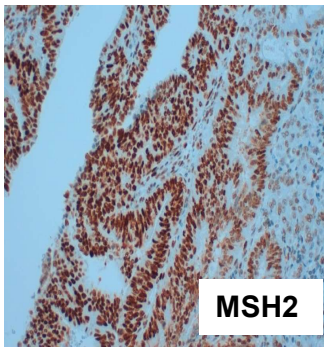
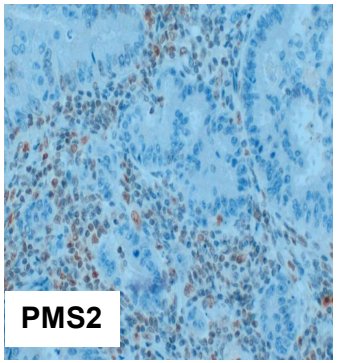
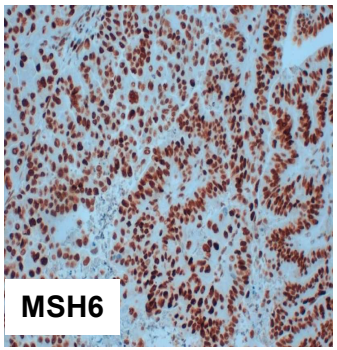
MMRD









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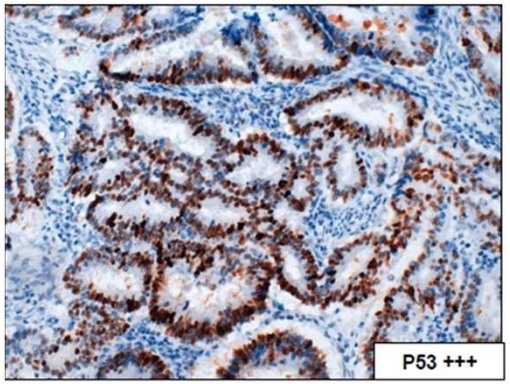

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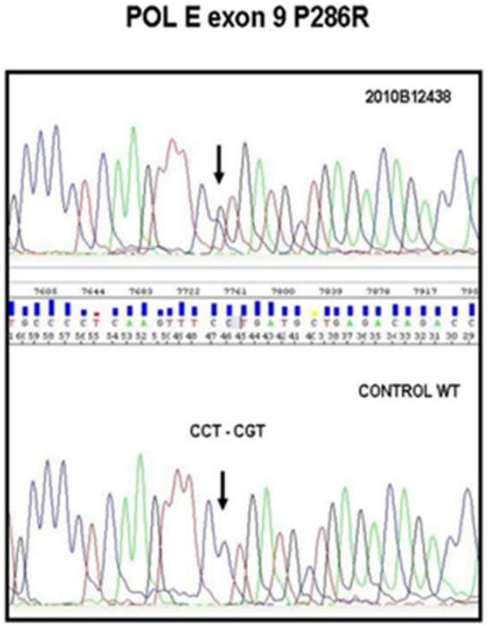

ESGO-ESTRO-ESP Guidelines
Endometrial Cancer 2020

ENGAGe
ESGO | European Network of Gynaecological Cancer Advocacy Groups

Virchows Archiv (2021) 478:153–190
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ORIGINAL ARTICLE

ESGO/ESTRO/ESP Guidelines for the management of patients with endometrial carcinoma

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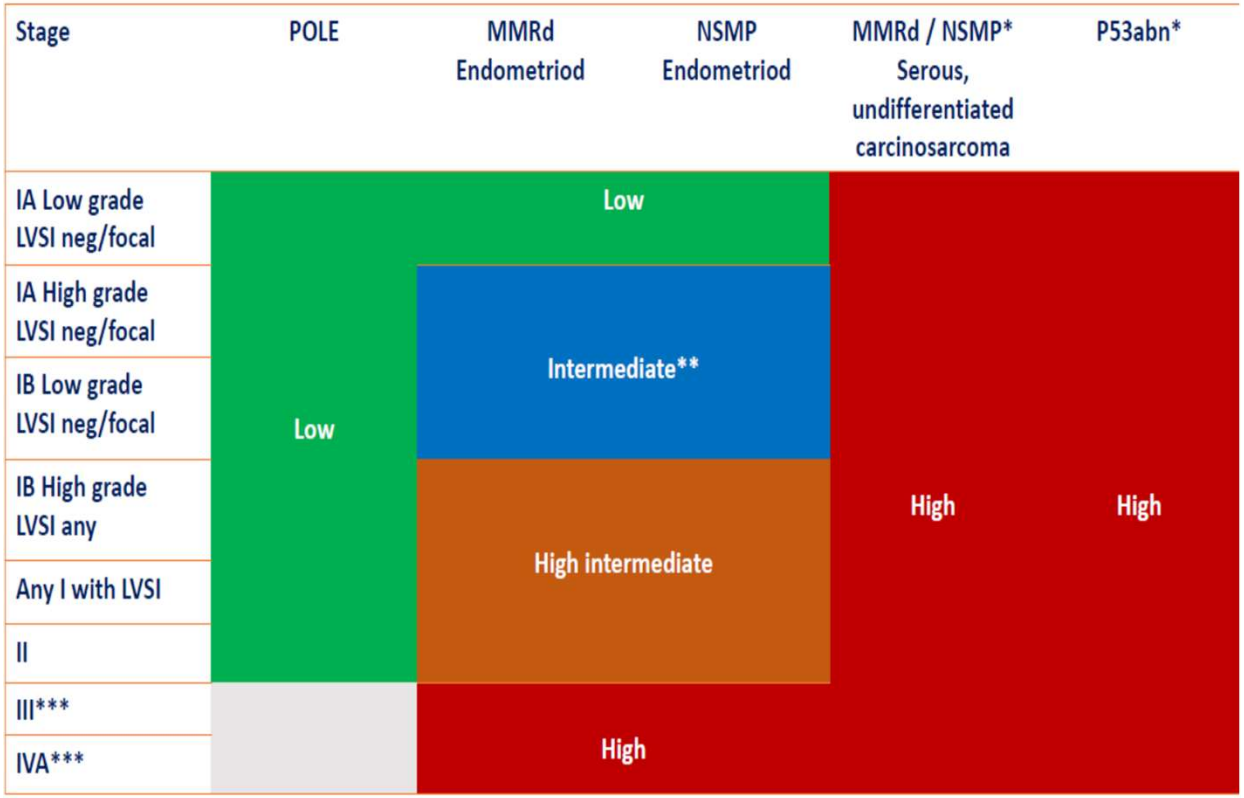
Abstract

A European consensus conference on endometrial carcinoma was held in 2014 to produce multidisciplinary evidence-based guidelines on selected questions. Given the large body of literature on the management of endometrial carcinoma published since 2014, the European Society of Gynaecological Oncology (ESGO), the European SocieTy for Radiotherapy & Oncology (ESTRO) and the European Society of Pathology (ESP) jointly decided to update these evidence-based guidelines and to cover new topics in order to improve the quality of care for women with endometrial carcinoma across Europe and worldwide. ESGO/ESTRO/ESP nominated an international multidisciplinary development group consisting of practicing clinicians and researchers who have demonstrated leadership and expertise in the care and research of endometrial carcinoma (27 experts across Europe). To ensure that the guidelines are evidence-based, the literature published since 2014, identified from a systematic search was reviewed and critically appraised. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group. The guidelines are thus based on the best available evidence and expert agreement. Prior to publication, the guidelines were reviewed by 191 independent international practitioners in cancer care delivery and patient representatives. The guidelines comprehensively cover endometrial carcinoma staging, definition of prognostic risk groups integrating molecular markers, pre- and intra-operative work-up, fertility preservation, management for early, advanced, metastatic, and recurrent disease and palliative treatment. Principles of radiotherapy and pathological evaluation are also defined.

PROGNOSTIC RISK GROUPS



*With myometrial invasion

**Stage IA p53abn and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasio

***No residual disease

FIGO staging of endometrial cancer: 2023

Jonathan S. Berek[1] | Xavier Matias-Guiu[2] | Carien Creutzberg[3] | Christina Fotopoulou[4] | David Gaffney[5] | Sean Kehoe[6] | Kristina Lindemann[7] | David Mutch[8] | Nicole Concin[9,10] | Endometrial Cancer Staging Subcommittee, FIGO Women's Cancer Committee

Int J Gynecol Obstet. 2023;162:383–394.

Endometrial carcinoma (Stage FIGO 1971)

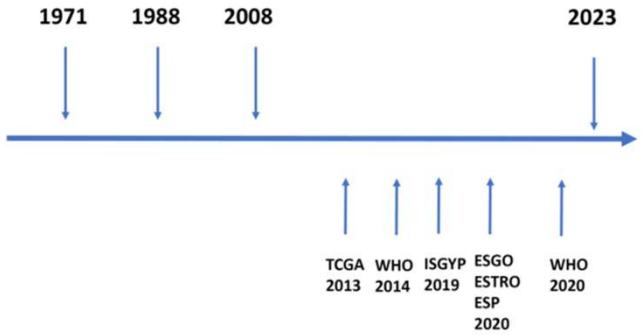
- 0: Carcinoma in situ
- I: Confined to the corpus
  - IA: lenght uterine cavity < 8 cm
  - IB: lenght uterine cavity > 8 cm
- II: Involving corpus and cervix
- III: Outside the uterus but not outside the true pelvis
- IV: outside the true pelvis, bladder or bowel mucosa

Endometrial carcinoma (Stage FIGO 1988)

- IA: limited to endometrium
- IB: < ½ myometrium
- IC: > ½ myometrium
- IIA: cervical glandular involvement
- IIB: cervical stromal invasion
- IIIA serosa, adnexae or peritoneal cytology
- IIIB vaginal involvement
- IIIC pelvic or para-aortic lymph nodes
- IVA bladder or bowel mucosa
- IVB distant metastasis

Endometrial carcinoma (Stage FIGO 2008)

- IA: limited to endometrium or < ½ myometrium
- IB: > ½ myometrium
- II: cervical stromal invasion
- IIIA serosa, and/or adnexae
- IIIB vaginal and/or parametrial involvement
- IIIC pelvic or para-aortic lymph nodes
  - 1- pelvic
  - 2- paraortic
- IVA bladder or bowel mucosa
- IVB distant metastasis



Pathological features

- Histologic Type and grade
- Myometrial invasion
- Lymphovascular space invasion (LVSI)
- Cervical Stromal invasion
- Adnexal involvement
- Uterine serosal involvement
- Lymph node status

- Molecular Classification

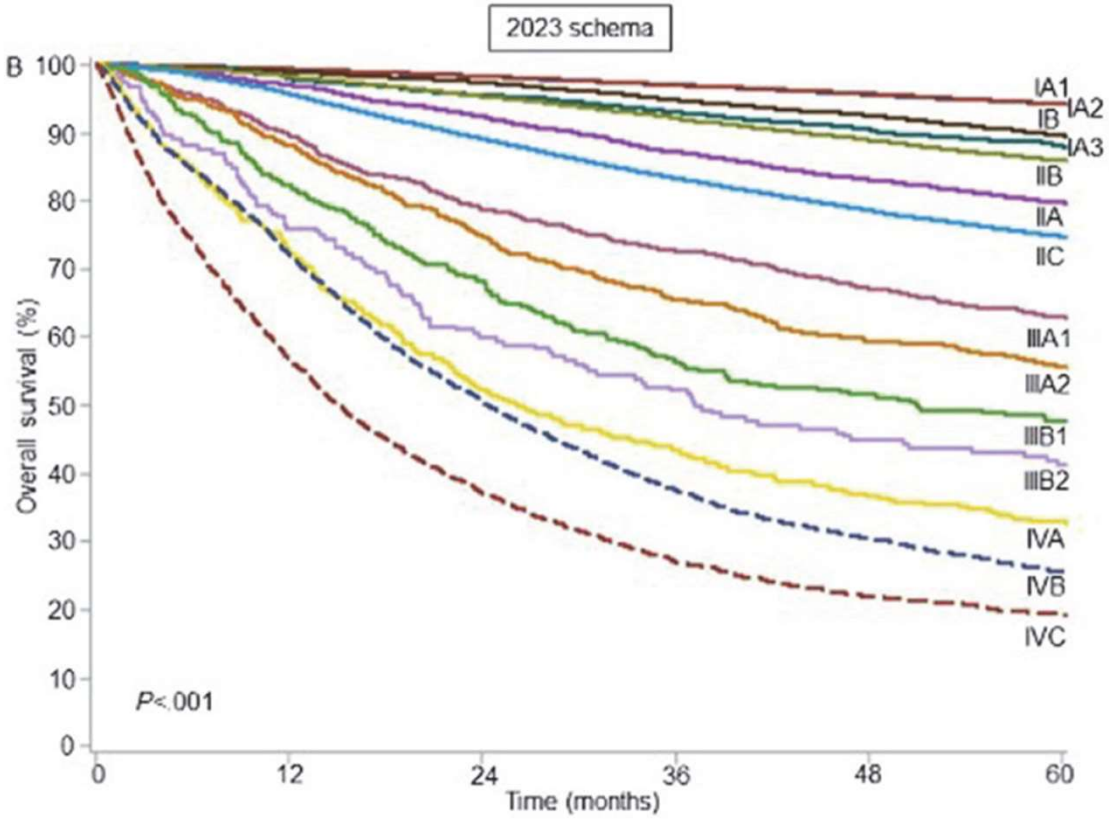
AS04. Endometrial/Uterine corpus cancers

SO023LBA/#1384 **PROGNOSTIC PERFORMANCE OF THE 2023 FIGO STAGING SCHEMA FOR ENDOMETRIAL CANCER**

[1]Hiroko Machida*, [2]Ling Chen, [3]Maximilian Klar, [2]Matthew Lee, [1]Mikio Mikami, [4]Laila Muderspach, [5]Joseph Carlson, [4]Lynda Roman, [4]Koji Matsuo, [6]Jason Wright. *[1]Tokai University School of Medicine, Obstetrics and Gynecology, Isehara, Japan; [2]Columbia University College of Physicians and Surgeons, Department of Obstetrics and Gynecology, New York, USA; [3]University of Freiburg Faculty of Medicine, Department of Obstetrics and Gynecology, Freiburg, Germany; [4]University of Southern California,, Gynecologic Oncology, Los angeles, USA; [5]University of Southern California,, Department of Pathology, Los angeles, USA; [6]Columbia University, Obstetrics and Gynecology, New York City, USA*

Introduction This study examined prognostic performance of the 2023 FIGO endometrial cancer staging schema.

Methods The National Cancer Database was retrospectively queried to examine 129,146 patients with stage I-IV endometrial cancer per the 2009 FIGO schema. Overall survival (OS) per the 2023 FIGO schema was assessed (figures 1–2).



What is a pathologist?
Final Conclusions

- The pathologist is important in gynecologic cancer
- Tissue handling is important
- Molecular analysis (HRD or molecular classification) has to be integrated with conventional pathologic analysis.

In the multidisciplinary tumor board (MTB), all Medical specialist (surgeons, medical oncologists, radiation oncologists, radiologists, nurses, and pathologists, discuss the best clinical management of the patient. The role of the pathologist is crucial in MTB.

The role of the pathologist in the diagnosis of gynecological cancer

January 31, 2023

Xavier Matias-Guiu,
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