ORIGIN AND STAGING OF TUBO-OVARIAN HIGH GRADE SEROUS CARCINOMAS

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IS TUBAL FIMBRIA THE ORIGIN OF EXTRAUTERINE HIGH GRADE SEROUS CARCINOMA?

- proposal that tubal fimbria (distal tube) (secretory cells) is site of origin of many/most extrauterine high grade serous carcinomas
- suggests that high grade serous carcinoma of ovary, peritoneum and fallopian tube are same neoplasm and many/most arise from tubal fimbria

Original Paper

Dysplastic changes in prophylactically removed Fallopian tubes of women predisposed to developing ovarian cancer

Jurgen M. J. Piek[1], Paul J. van Diest[2]*, Ronald P. Zweemer[1], Jan W. Jansen[3], Ria J. J. Poort-Keesom[1], Fred H. Menko[4], Johan J. P. Gille[4], Ans P. M. Jongsma[1], Gerard Pals[4], Peter Kenemans[1] and René H. M. Verheijen[1]

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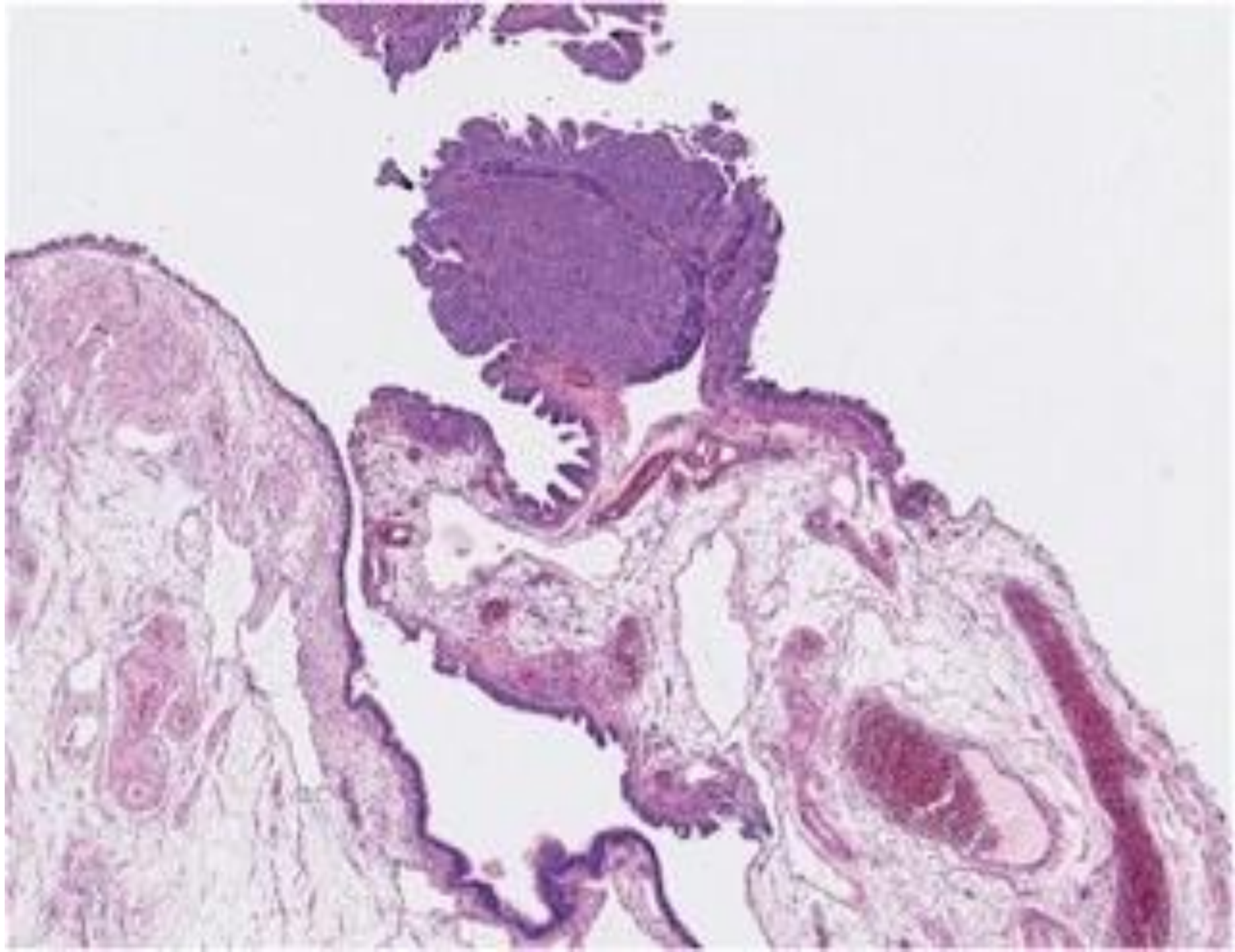
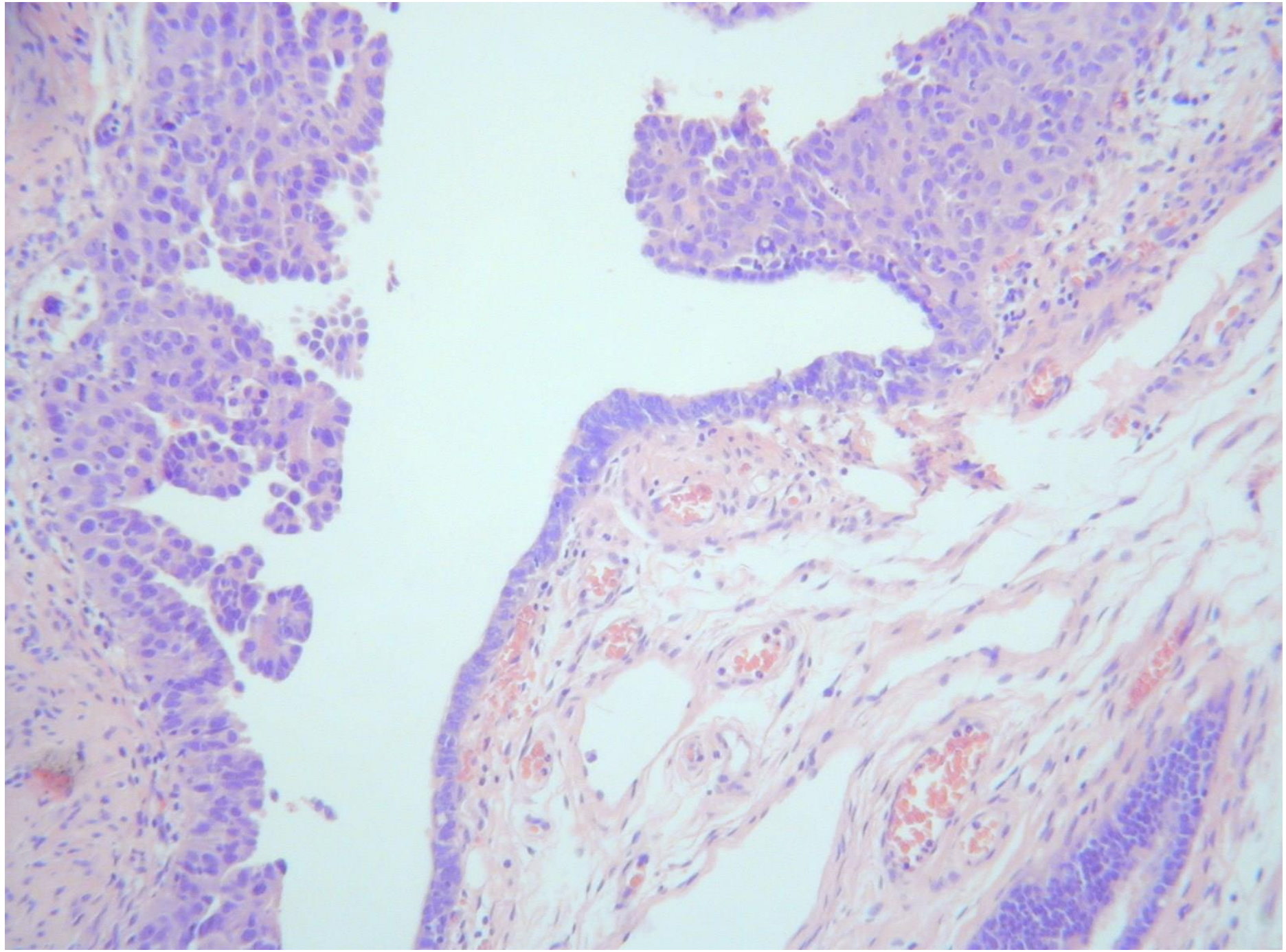
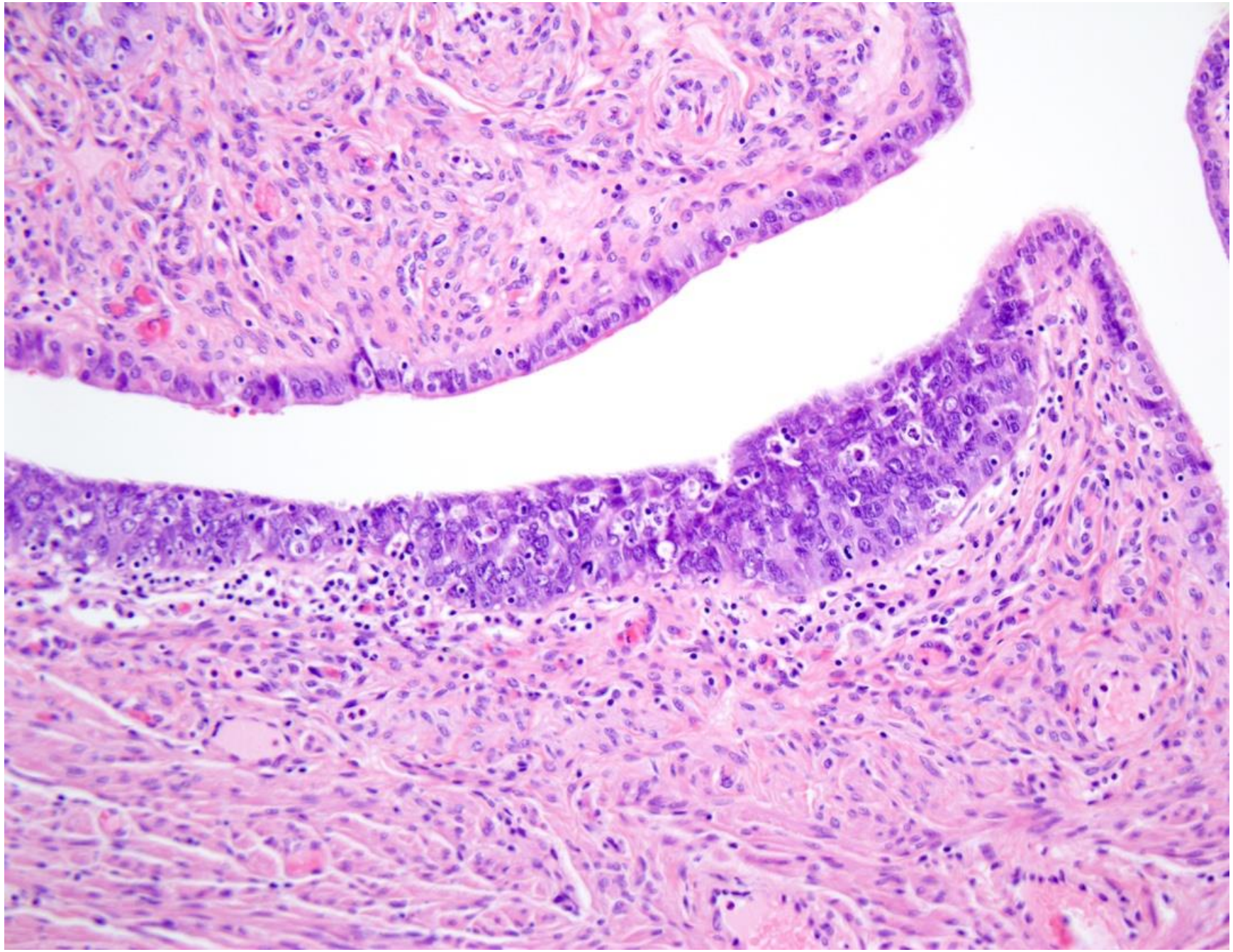
J Pathol 2001; **195**: 451–456.

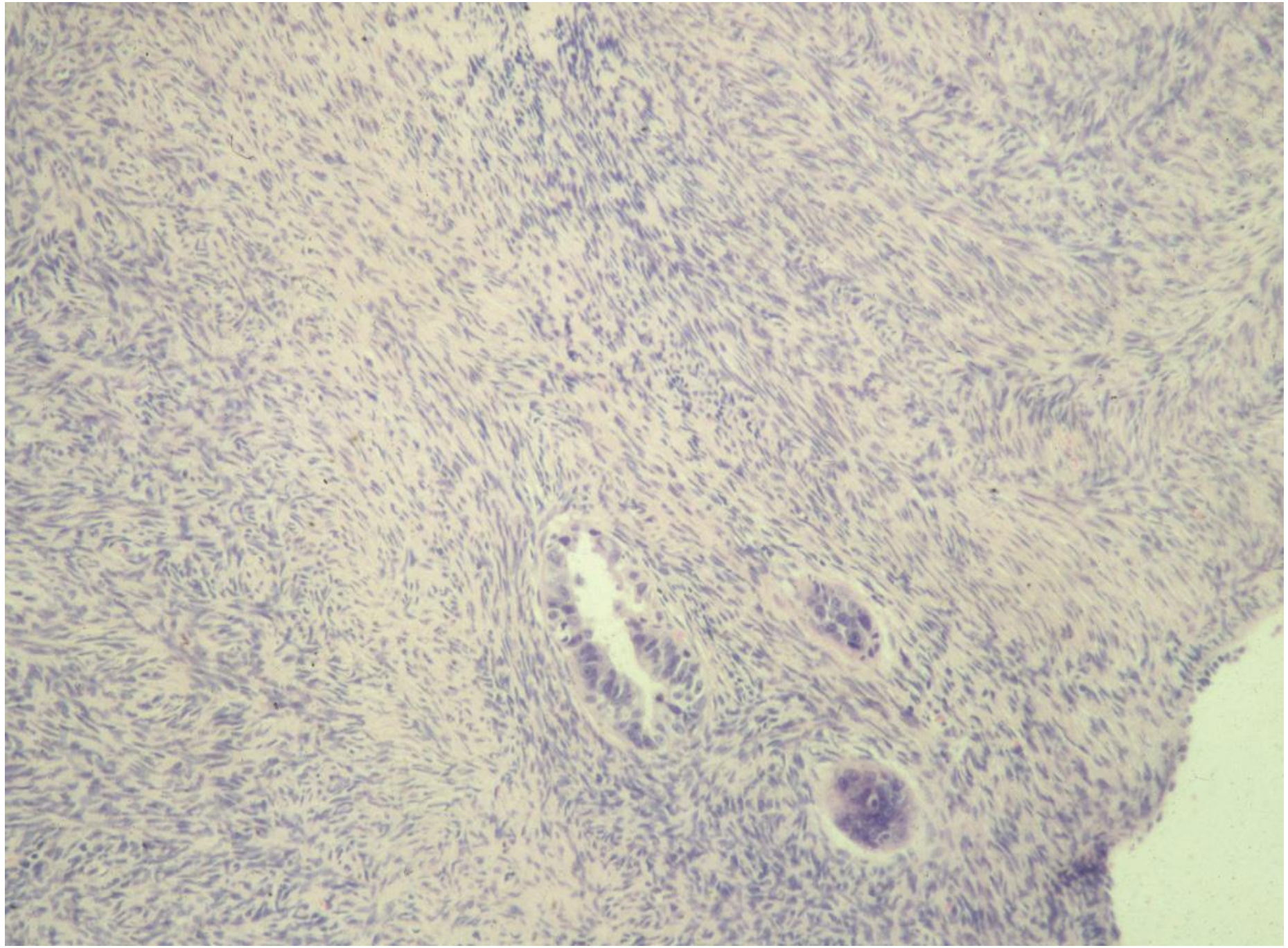
INITIAL EVIDENCE

- came from prophylactic risk reducing salpingo-oophorectomy specimens (RRSO) (BRCA1/2)
- once tubes were examined in their entirety, tubal lesions (distal) were seen with little/ nothing in ovary
- tubal lesions may be STIC (serous tubal intraepithelial carcinoma) or small HGSCs
- now well established in BRCA patients that tube is origin of HGSCs
- ? does same hold true for sporadic HGSCs

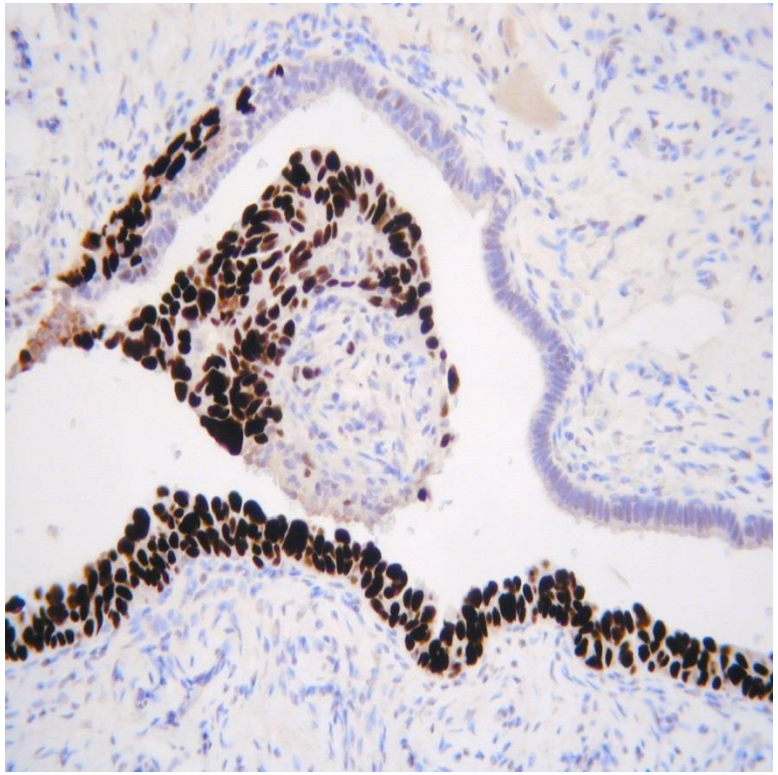


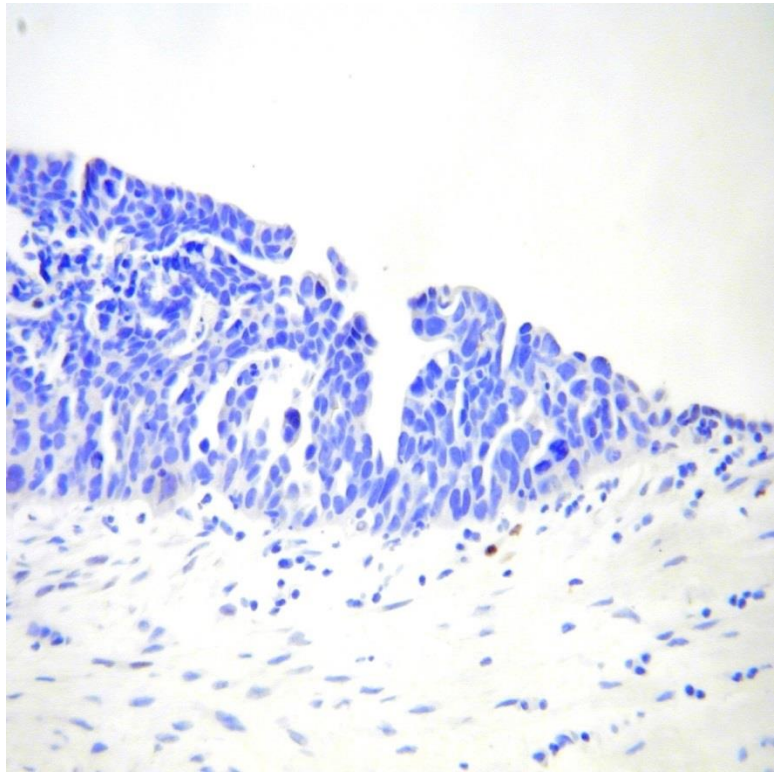




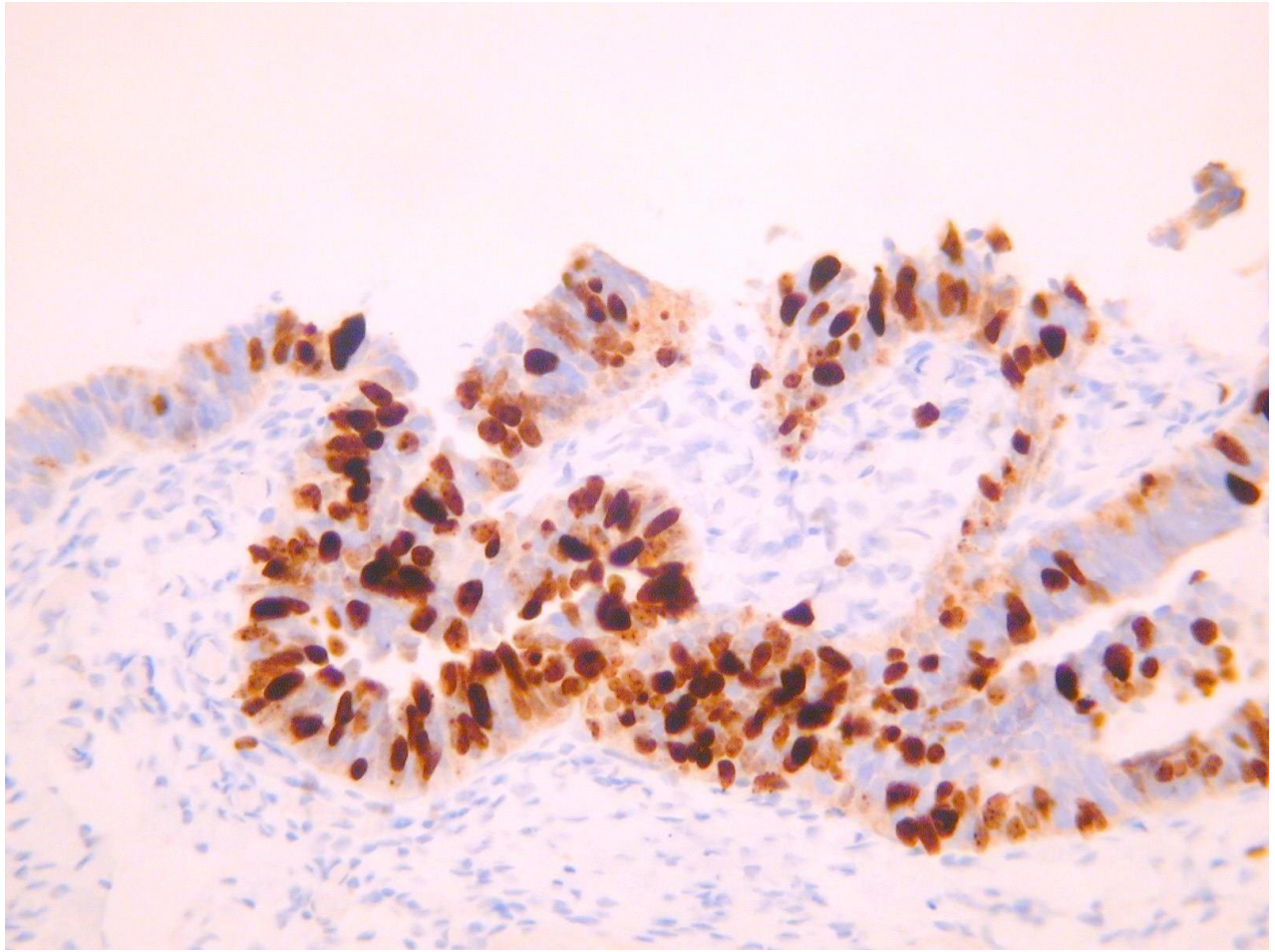


p53 in STIC





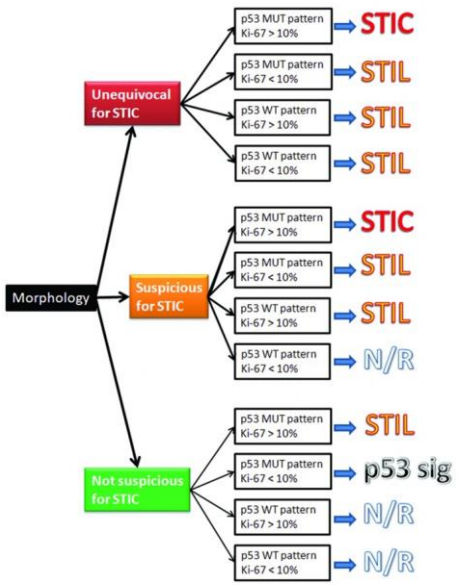
MIB1 IN STIC



OVERDIAGNOSIS OF STIC

- increasing scrutiny on tubal epithelium
- normal tubal epithelium can be “atypical”- variation in nuclear size, loss of polarity- especially premenopasual
- cautery artefact
- to diagnose STIC- need morphological changes (definite) supported by p53 and MIB1 in problematic cases
- don’t report changes “less than” STIC (unless in research setting)
- don’t do p53 routinely (p53 signatures)

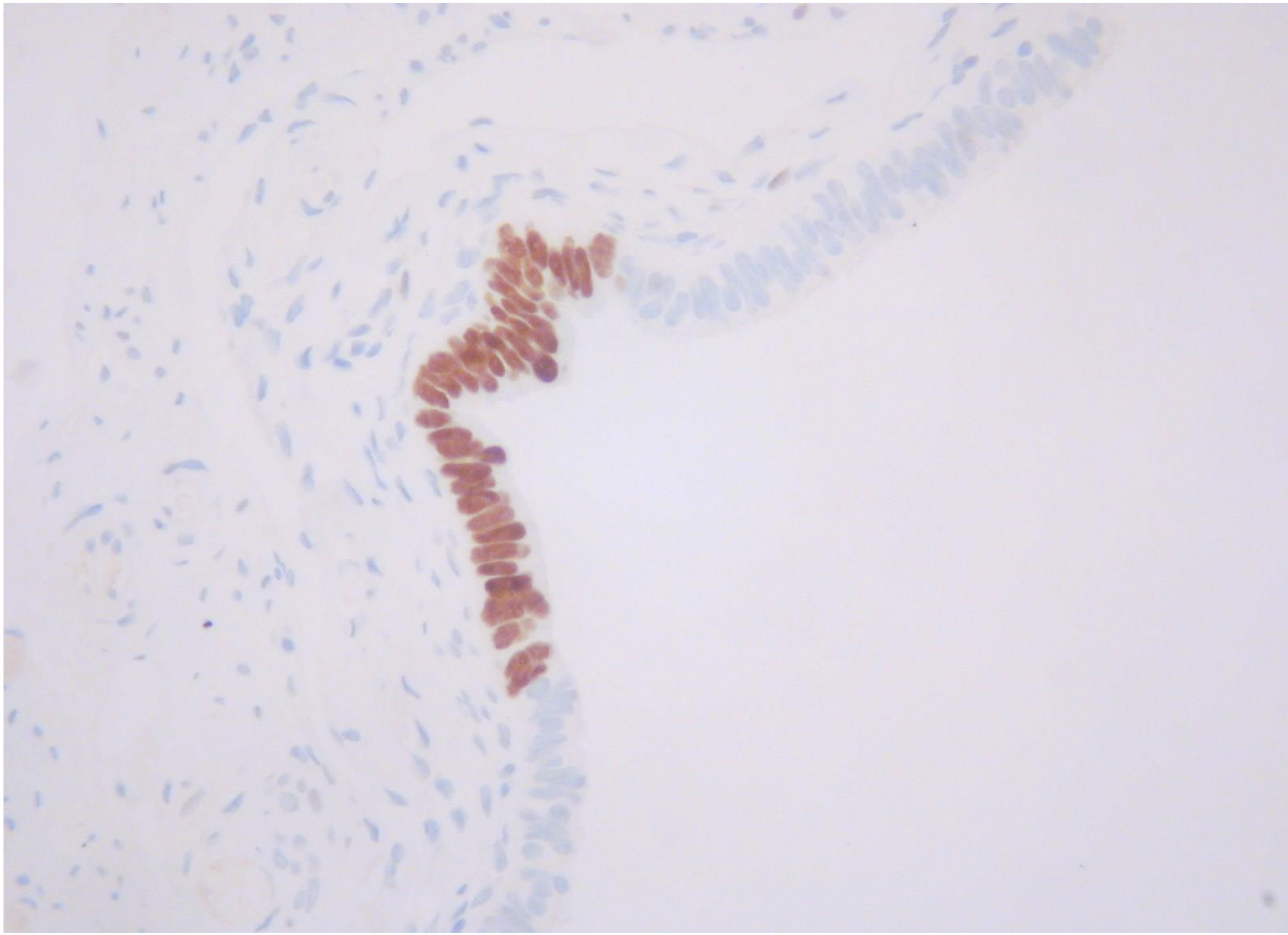
Implications for pathological diagnosis



- STIC must be diagnosed with care using defined criteria
- p53 and Ki67 IHC required for confirmation and exclusion of mimics
- benign mimics which can result in overdiagnosis

p53 SIGNATURES IN TUBE

- small foci of intense p53 immunoreactivity in absence of morphological changes
- equally common in BRCA1/2 tubes and in control tubes (occur in all age groups)
- most common in fimbria
- involves secretory cells
- may contain *Tp53* mutations (? occurring all the time, ? need second event)
- don’t diagnose STIC in isolation in absence of morphological features and confirmatory p53 and MIB1



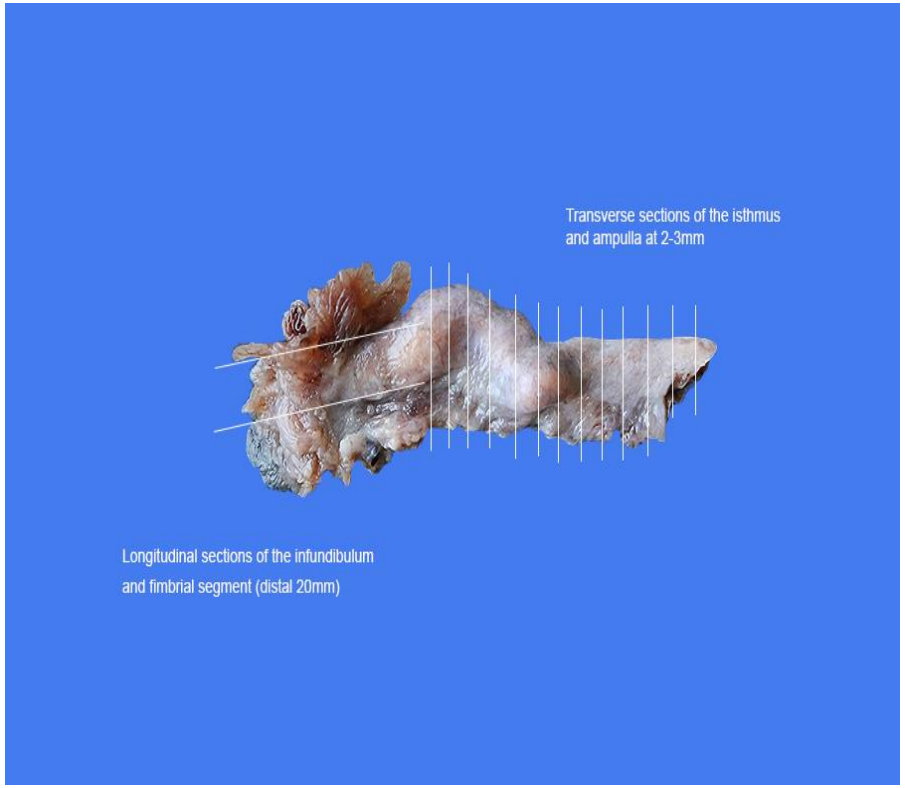
p53

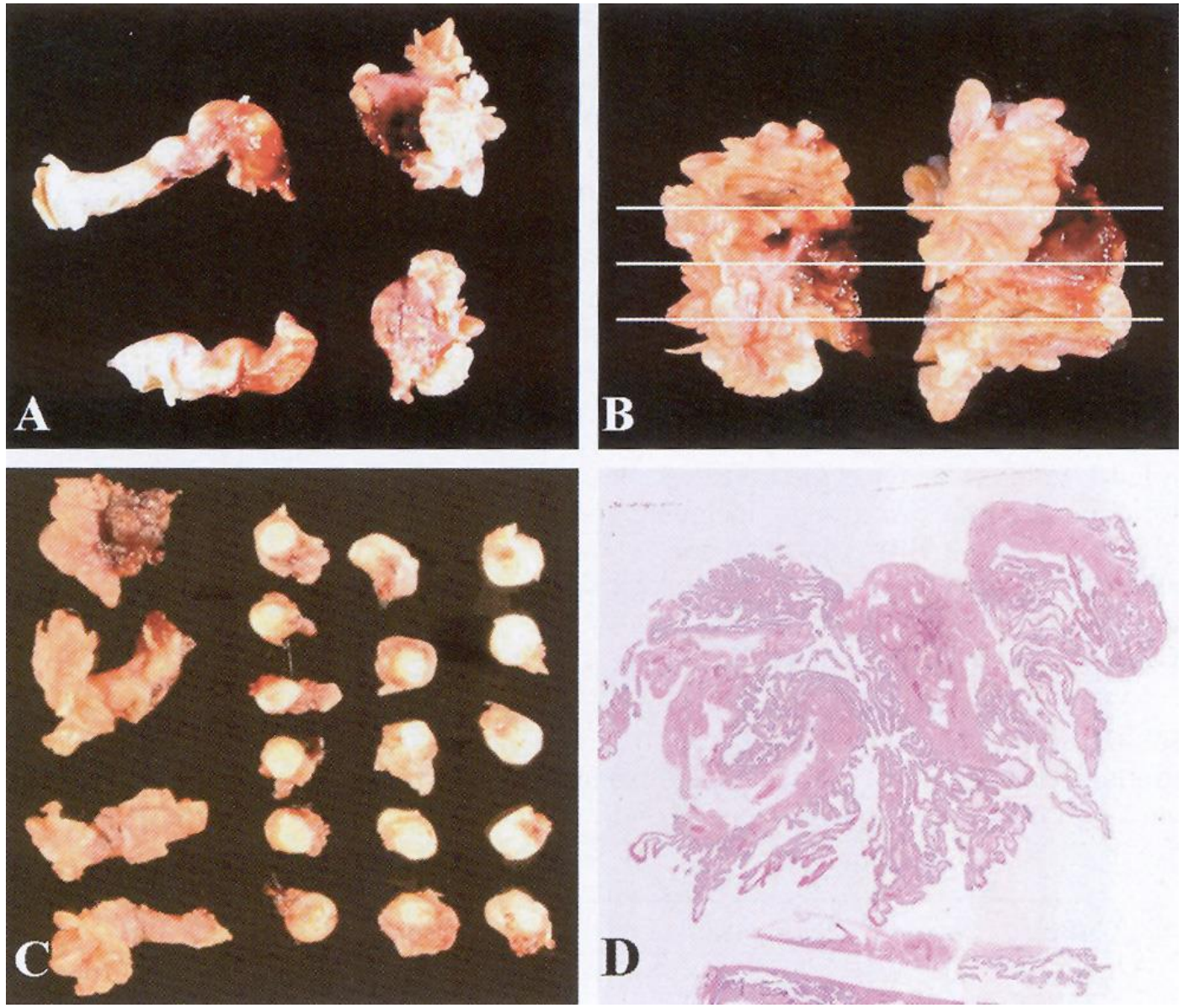
WHAT ABOUT SPORADIC HGSCs

- Usually present at advanced stage
- Tube (s) often obliterated and embedded in tubo-ovarian mass
- Difficult to study precursor lesions
- STIC/ mucosal HGSC found in carefully sectioned tubes (when both visible) in significant percentage of cases (up to two-thirds) of sporadic HGSC

Implications for specimen handling

- SEE-FIM protocol ESSENTIAL for identifying STIC/early tubal involvement




A
B
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Pathological findings in women with known BRCA1/2 mutation

Pathology protocol Y/N	BRCA carriers (n)	Neoplasia (n)	Rate of neoplasia (%)	Neoplasia in tube (n)
Studies without specified pathology protocol/non-standard protocol	500	10	2.0	2
Studies with specified pathology protocol	381	31	8.1	16

Gross et al, J Oncol 2010

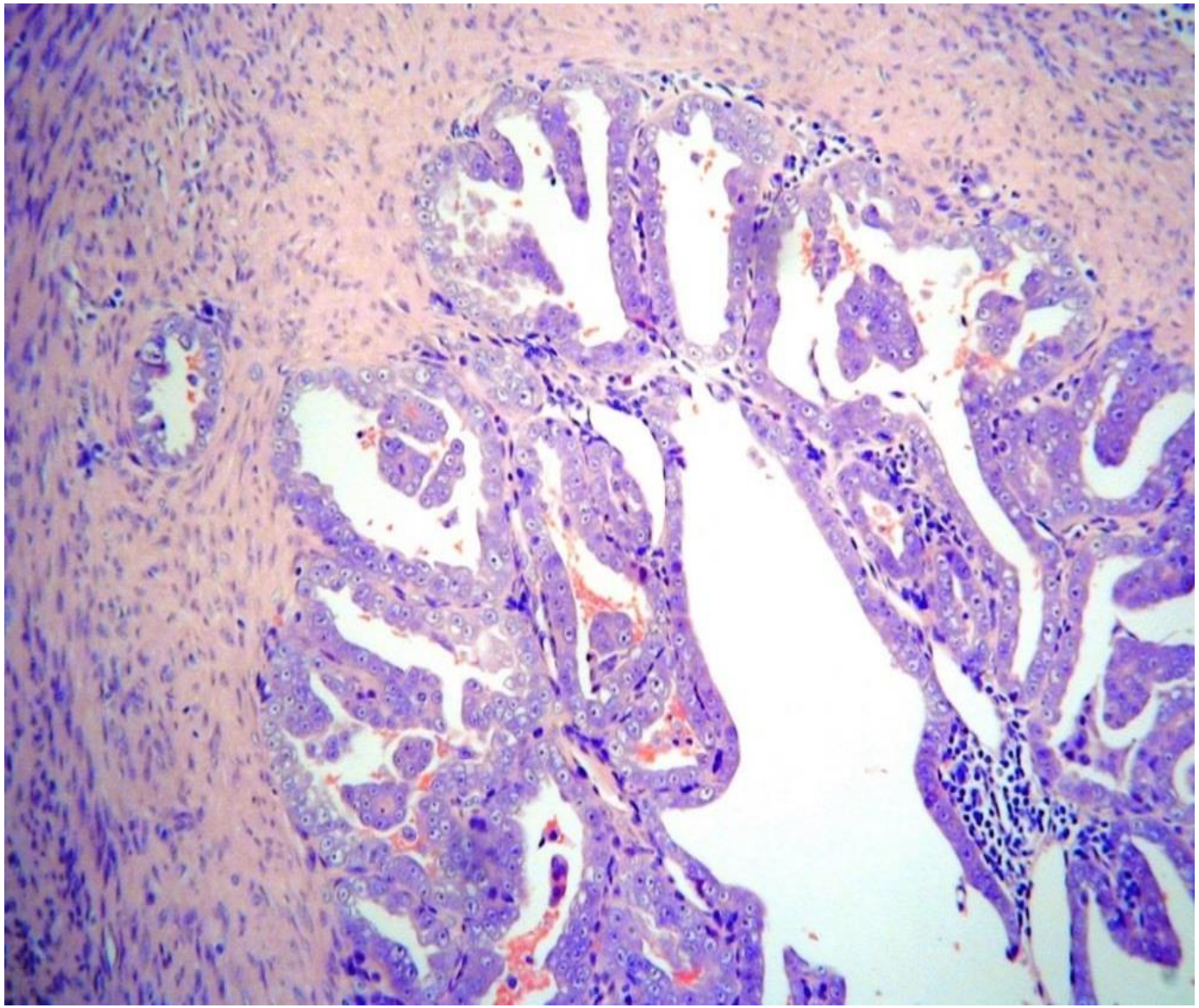
? FIELD-EFFECT IN HGSC

- same *TP53* mutations in HGSC at multiple sites
- evidence that clonally related and not part of “field-effect”
- no evidence of field-effect in HGSC
- one site is primary with metastasis to the others
- other molecular evidence- common clonal ancestry at multiple sites

BUT IS TUBAL LESION PRIMARY OR METASTATIC?

- Intramucosal metastasis from a variety of sites may occur in tubes and mimic an in-situ lesion
- Some molecular evidence that tube is initial site but difficult to prove by molecular techniques
- RECENT OBSERVATIONAL STUDIES PROVIDE FIRM EVIDENCE

USC INVOLVING FALLOPIAN TUBE



INCIDENTAL SPORADIC HIGH GRADE SEROUS CARCINOMA

- established that incidental tumours in patients with BRCA1/2 mutation are of tubal origin
- 3 papers recently published- unsuspected STIC/ HGSC incidentally detected (ours= AJSP 2015; 39; 357- 364)
- PROVES that sporadic HGSC of tubal origin (FINAL PIECE OF EVIDENCE)

Incidental Nonuterine High-grade Serous Carcinomas Arise in the Fallopian Tube in Most Cases

Further Evidence for the Tubal Origin of High-grade Serous Carcinomas

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Am J Surg Pathol, 2014

Incidental Serous Tubal Intraepithelial Carcinoma and Early Invasive Serous Carcinoma in the Nonprophylactic Setting

Analysis of a Case Series

Jane C. Morrison, MD, Luis Z. Blanco, Jr, MD,* Russell Vang, MD,*† and Brigitte M. Ronnett, MD*†*

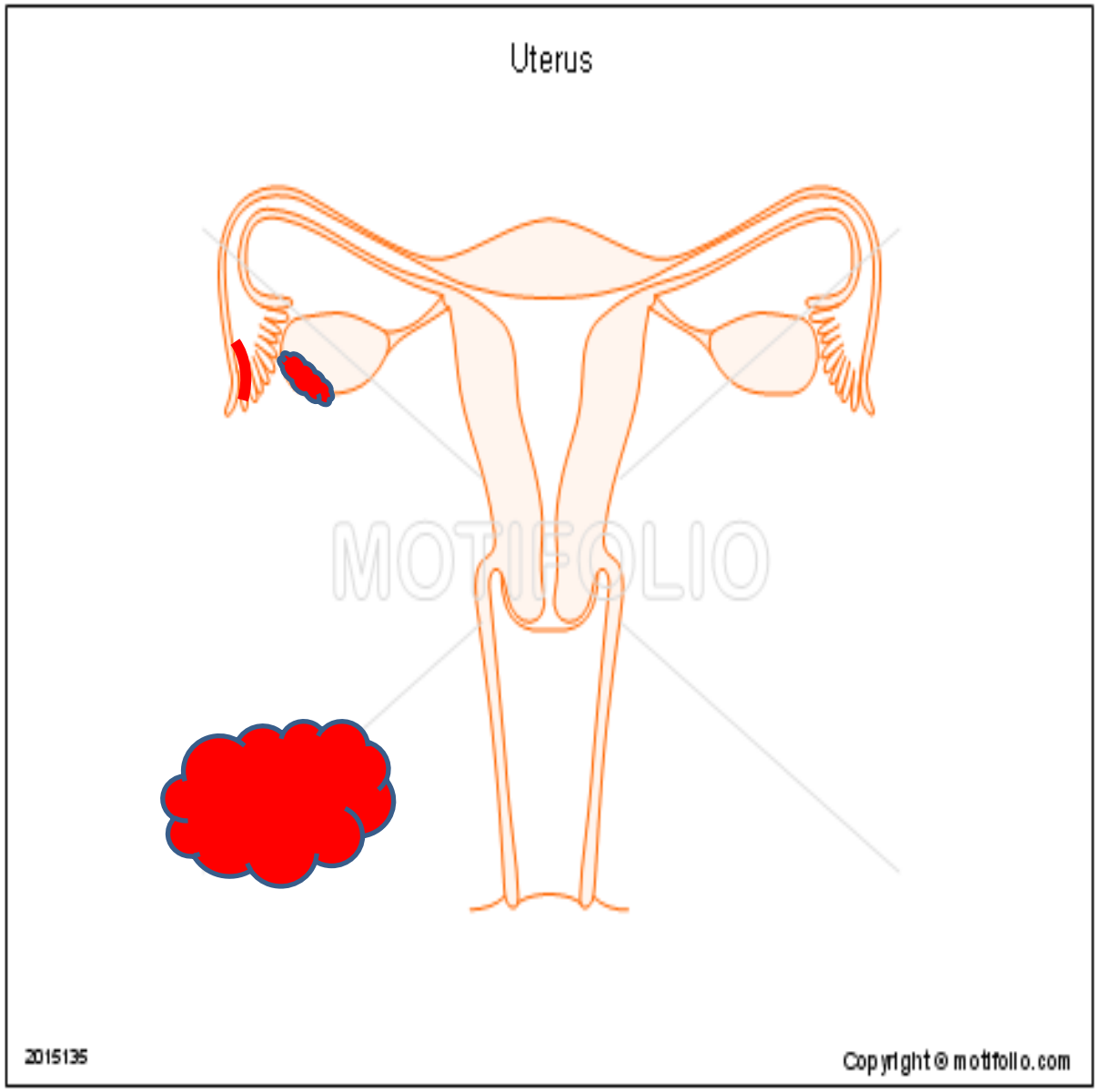
Am J Surg Pathol, 2014

Summary of findings of incidental HGSC in a non-prophylactic setting

Study	Total cases	Cases with STIC	Invasive HGSC in tube	Invasive HGSC in ovary	Organ-confined Disease (tube OR ovary)	Organ-confined: tube	Organ-confined: ovary
Rabban, 2014	4	4	3	1	3	3	0
Morrison, 2014	22	22	6	1	21	21	0
Gilks, 2014	21	20	12	2	18	18	0
Total	**47**	**47**	**22**	**4**	**43**	**43**	**0**

EXTRAUTERINE HIGH GRADE SEROUS CARCINOMA- SITE OF ORIGIN

- FIGO 2014- same staging system (ovary, tube, peritoneum, undesignated)
- FIGO 2014 and WHO 2014- no recommendations regarding designating site of origin
- WHO- the decision as to primary site should be pragmatic, based on experience and professional judgement
- DOMINANT MASS THEORY TRADITIONALLY USED (ovary designated as primary site in most cases)
- possibilities- pelvic high grade serous; extrauterine; Mullerian; tubo-ovarian; undesignated
- implications:- epidemiology, tumour incidence/mortality, cancer registries, entry into clinical trials
- different viewpoints- STIC/ in situ criteria; dominant mass criteria



Ovarian?
Peritoneal?
Tubal?
Undesignated?

…. CHAOS!

SURVEY: INTERNATIONAL JOURNAL OF GYNECOLOGICAL PATHOLOGY – PMID 27801755

- 173 respondents
- Widespread acceptance of tubal origin (86% pathologists, 92% clinicians)
- Clinicians thought it more important to correctly assign a primary site than pathologists (71% versus 49%)

What FIGO stage would you assign in a case showing STIC with invasive HGSC in one ovary and no other disease site?

- Pathologists- primary tube stage II (45%); primary ovary stage I (27%)
- Clinicians- primary tube stage II (37%); primary ovary stage I (37%)
- FIGO- bilateral tubal involvement (very rare scenario)- stage IB (should really be stage II)

PROPOSAL FOR DESIGNATING SITE OF ORIGIN OF HGSC

- extensive examination of tube (SEE-FIM)
- any STIC or mucosal serous ca in tube- tubal origin
- if fallopian tube or fimbria not identified (obliterated by mass)- tubal origin
- ovarian primary if tumour in ovary and nothing in mucosa of tube (STIC or invasive) (both tubes need to be clearly visible and examined by SEE-FIM protocol)
- primary peritoneal- nothing in tube or ovary (vanishingly rare- will likely disappear) (WHO 2014)
- post-chemo (if no residual) or on small biopsy- designate as tubo-ovarian
- USING THESE CRITERIA- approximately 80% tubal primaries
- undesignated- very small proportion
- (Histopathology 2014; 65; 149-154; Gynecological Oncology 2016;141;195-198; International Journal of Gynecological Pathology 2016;35;230-237)

Summary of site assignment guidelines proposals

Criteria	Primary site	Comment
STIC present	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
Invasive mucosal carcinoma in tube, with or without STIC	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
Distal end or entire tube incorporated into ovarian mass	Fallopian tube	Regardless of presence and size of ovarian and peritoneal disease
No STIC or invasive mucosal carcinoma in either tube in presence of ovarian mass	Ovary	Regardless of presence and size of peritoneal disease
Both tubes and both ovaries grossly and microscopically normal or involved by benign process in presence of peritoneal HGSC	Primary peritoneal HGSC	As recommended in WHO blue book 2014[57]

Application of site assignment to a case series

ASSESSMENT OF A NEW SYSTEM FOR PRIMARY SITE ASSIGNMENT IN HIGH-GRADE SEROUS CARCINOMA OF FALLOPIAN TUBE, OVARY AND PERITONEUM

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Histopathology 2015; 67; 331-337

	RETROSPECTIVE (n=151)				PROSPECTIVE (n=111)			
Primary site	T	O	P	U	T	O	P	U
Chemo naive	63 **(79%)**	16 (20%)	0 (0%)	1 (1%)	44 **(83%)**	9 (17%)	0 (0%)	0 (0%)
Post-NACT	48 **(68%)**	16 (22%)	7 (10%)	0 (0%)	44 **(76%)**	7 (12%)	4 (7%)	3 (5%)

Singh et al, 2015

Basis for tubal assignment in 44 chemonaive cases

Criterion	Number (%)
STIC only	5 (11%)
Invasive mucosal +/- STIC	26 (59%)
Entire tube or part of tube incorporated in mass	13 (30%)
Total	44

Singh et al, 2015

Results (reproducibility)

- Four of four reviewing pathologists agreed on site assignment in 45/50 (90%) of cases
- Three of four reviewing pathologists agreed on site assignment in 49/50 (98%) of cases

Unilateral vs bilateral tubal and ovarian involvement in HGSC

	Unilateral	Bilateral	Total
Ovary	18 (38%)	**29 (62%)**	47
Fallopian tube	**37 (84%)**	7 (16%)	44

- Bilaterality = strong indicator of secondary spread
- In 53 chemo-naïve cases, ovarian involvement in HGSC was significantly more frequently bilateral
- Tubal involvement unilateral in 84% supporting primary rather than metastatic involvement

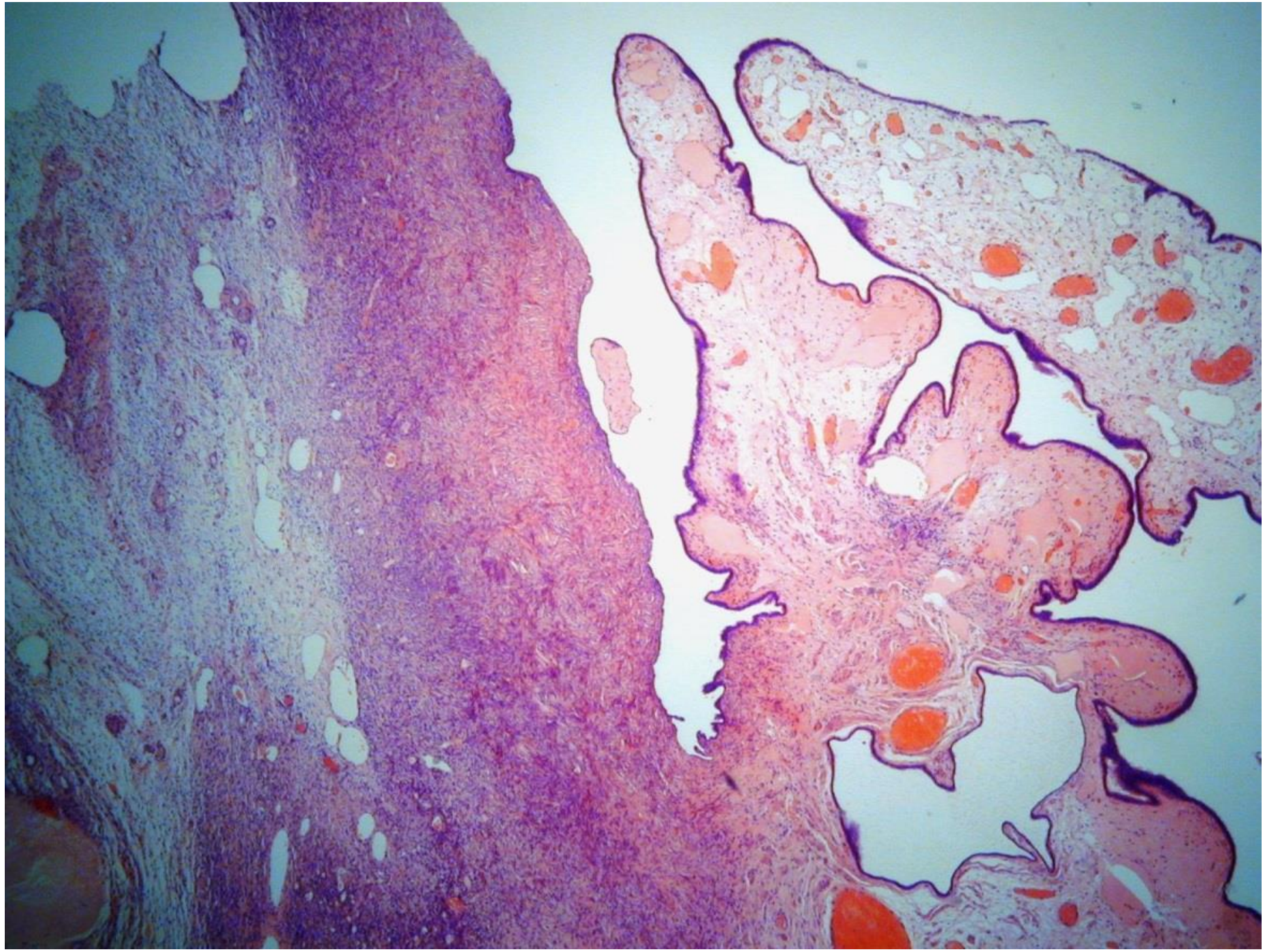
Singh et al, 2015

General implications

- Consistency and uniformity in reporting and in message to patients
- Tumour registry data
- Sharing data and good practice

SALPINGECTOMY WITHOUT OOPHORECTOMY

- Theoretically salpingectomy and delayed oophorectomy in high risk patients; to preserve hormonal function
- Need studies to evaluate safety
- Opportunistic salpingectomy
- However, some HGSCs probably arise in ovary (from tubal-type epithelium)



Conclusions

- Majority of extrauterine HGSC, hereditary and sporadic, arise in the fallopian tube, mostly its fimbrial end
- Multiple sites of HGSC arise from a single ancestral clone
- Molecular evidence does not support the concept of multifocal origin
- Primary peritoneal HGSC can only be diagnosed if both tubes and both ovaries show no STIC/HGSC
- Following a defined protocol results in reproducible site assignment
- Thus assigned, sporadic HGSC shows a similar site distribution to hereditary cases
- Witnessing a major paradigm shift
- ACCEPTABLE TO CALL TUBO-OVARIAN HGSC

DIFFERENCES BETWEEN USC AND TUBAL HGSC

- look the same, *TP53* mutations ubiquitous

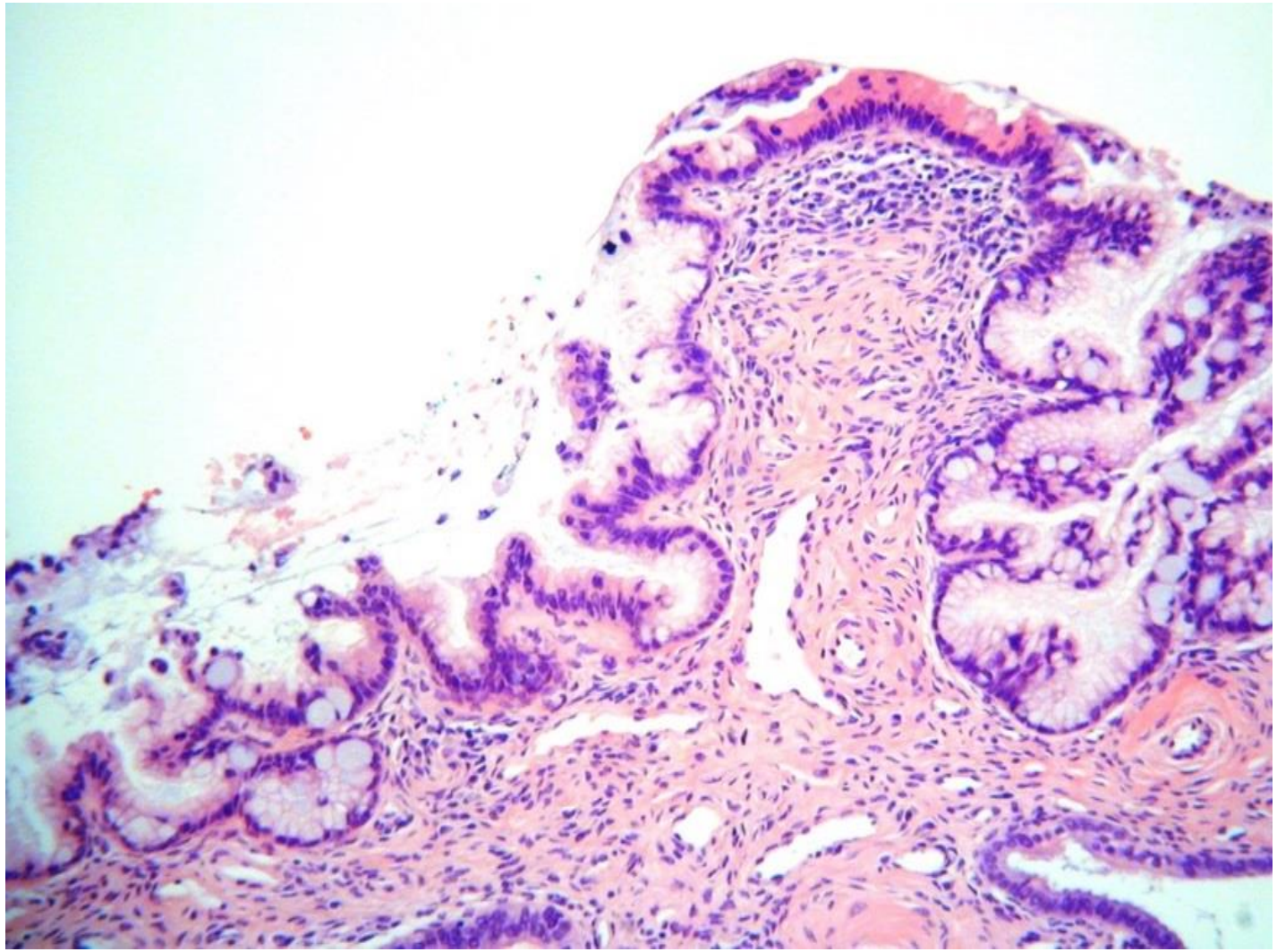
DIFFERENCES

- Uterine less chemosensitive
- WT1, ER staining
- BRCA abnormalities- tubal
- PPP2RIA mutations much more in uterine

TUBAL INVOLVEMENT IN ENDOMETRIAL SEROUS CARCINOMA

- May mimic STIC (STIC is usually, but not always, fimbrial)
- Gynaecological or non-gynaecological tumours when spread to tube exhibit mucosal involvement and even mimic STIC (AJSP 2015;39;35-51)

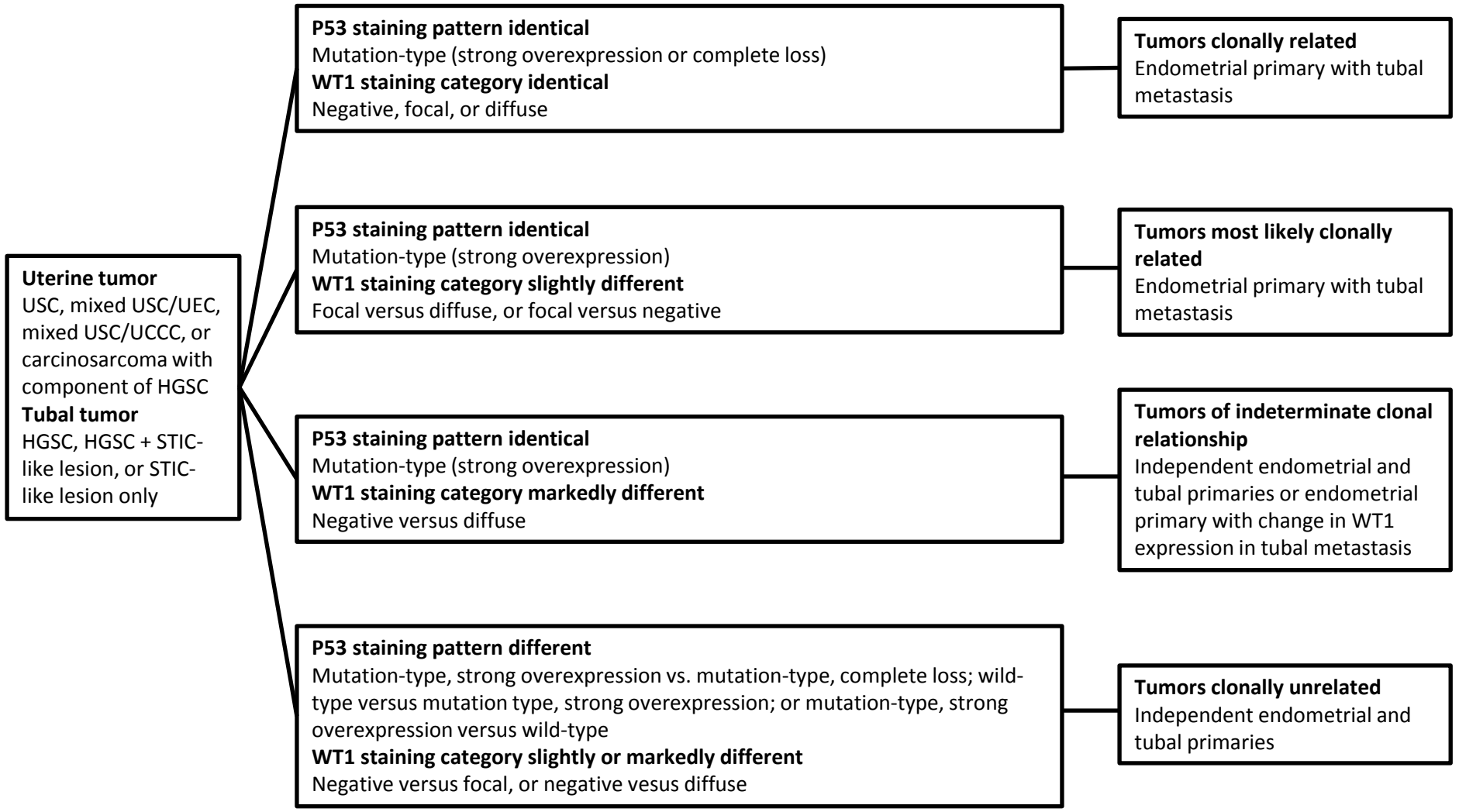
GASTRIC TYPE CERVICAL ADENOCA INVOLVING TUBE



AJSP 2017;41;161-170

- 161 consecutive cases collected at author's institutions
- pure endometrial serous carcinoma, mixed carcinomas with component of serous carcinoma, carcinosarcomas with component of serous carcinoma
- fallopian tubes examined in their entirety using a SEE-FIM protocol
- WT1 and p53 staining done in cases with both uterine and tubal involvement
- patterns of p53 staining: strong overexpression, complete loss (both mutation-type); focal (wild-type)
- WT1 staining categories: negative (0% positive cells); focal (1-50% of positive cells); and diffuse (>50% of positive cells)

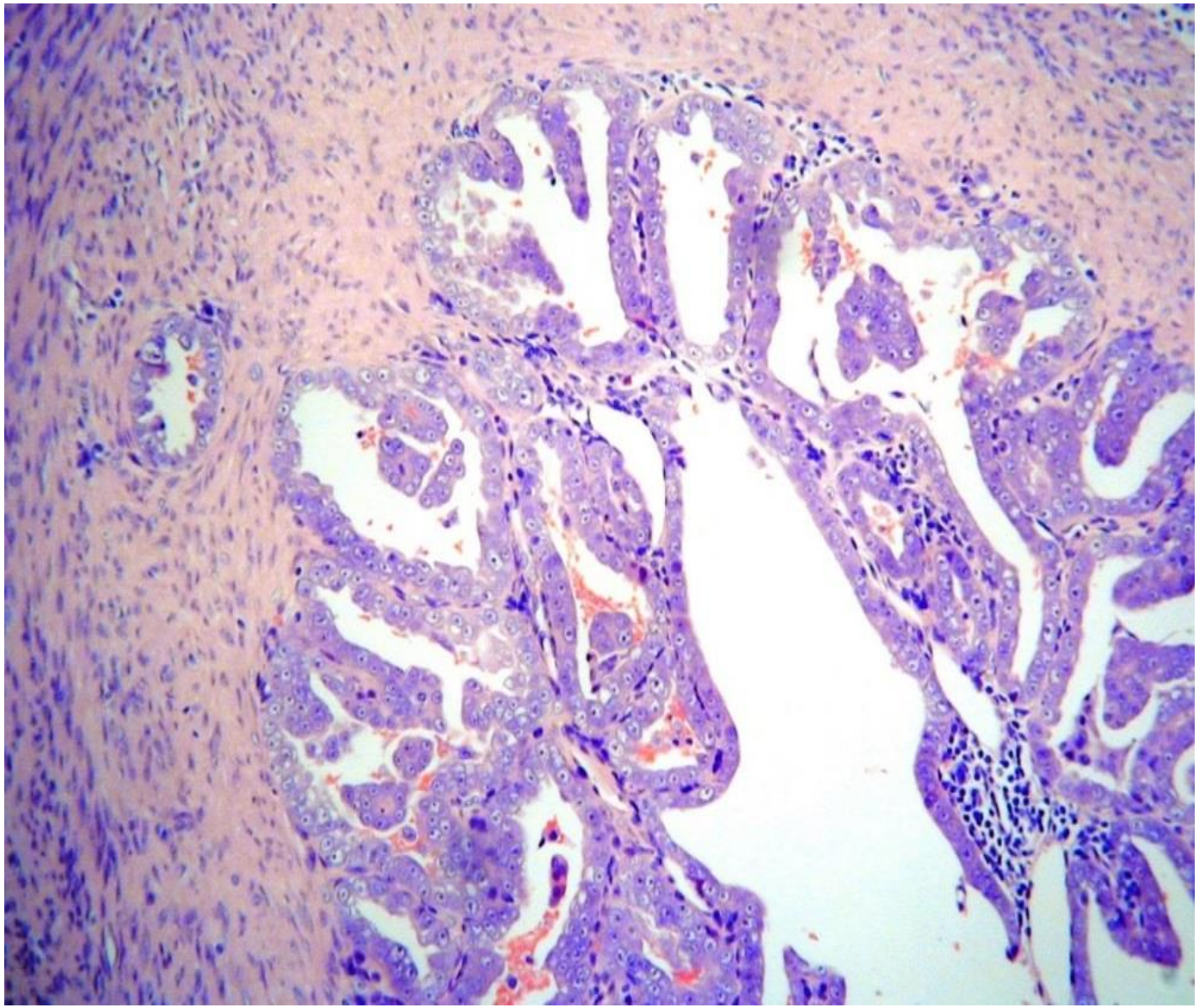
ASSESSMENT


Uterine tumor
USC, mixed USC/UEC, mixed USC/UCCC, or carcinosarcoma with component of HGSC
Tubal tumor
HGSC, HGSC + STIC-like lesion, or STIC-like lesion only
P53 staining pattern identical
Mutation-type (strong overexpression or complete loss)
WT1 staining category identical
Negative, focal, or diffuse
Tumors clonally related
Endometrial primary with tubal metastasis
P53 staining pattern identical
Mutation-type (strong overexpression)
WT1 staining category slightly different
Focal versus diffuse, or focal versus negative
Tumors most likely clonally related
Endometrial primary with tubal metastasis
P53 staining pattern identical
Mutation-type (strong overexpression)
WT1 staining category markedly different
Negative versus diffuse
Tumors of indeterminate clonal relationship
Independent endometrial and tubal primaries or endometrial primary with change in WT1 expression in tubal metastasis
P53 staining pattern different
Mutation-type, strong overexpression vs. mutation-type, complete loss; wild-type versus mutation type, strong overexpression; or mutation-type, strong overexpression versus wild-type
WT1 staining category slightly or markedly different
Negative versus focal, or negative vesus diffuse
Tumors clonally unrelated
Independent endometrial and tubal primaries

RESULTS

- tubal involvement: 32/161 (20%)
- cases with tubal involvement: deep myometrial invasion and LVSI more frequently present as compared to cases without (72% versus 48% and 59% versus 45%, respectively)

USC INVOLVING FALLOPIAN TUBE



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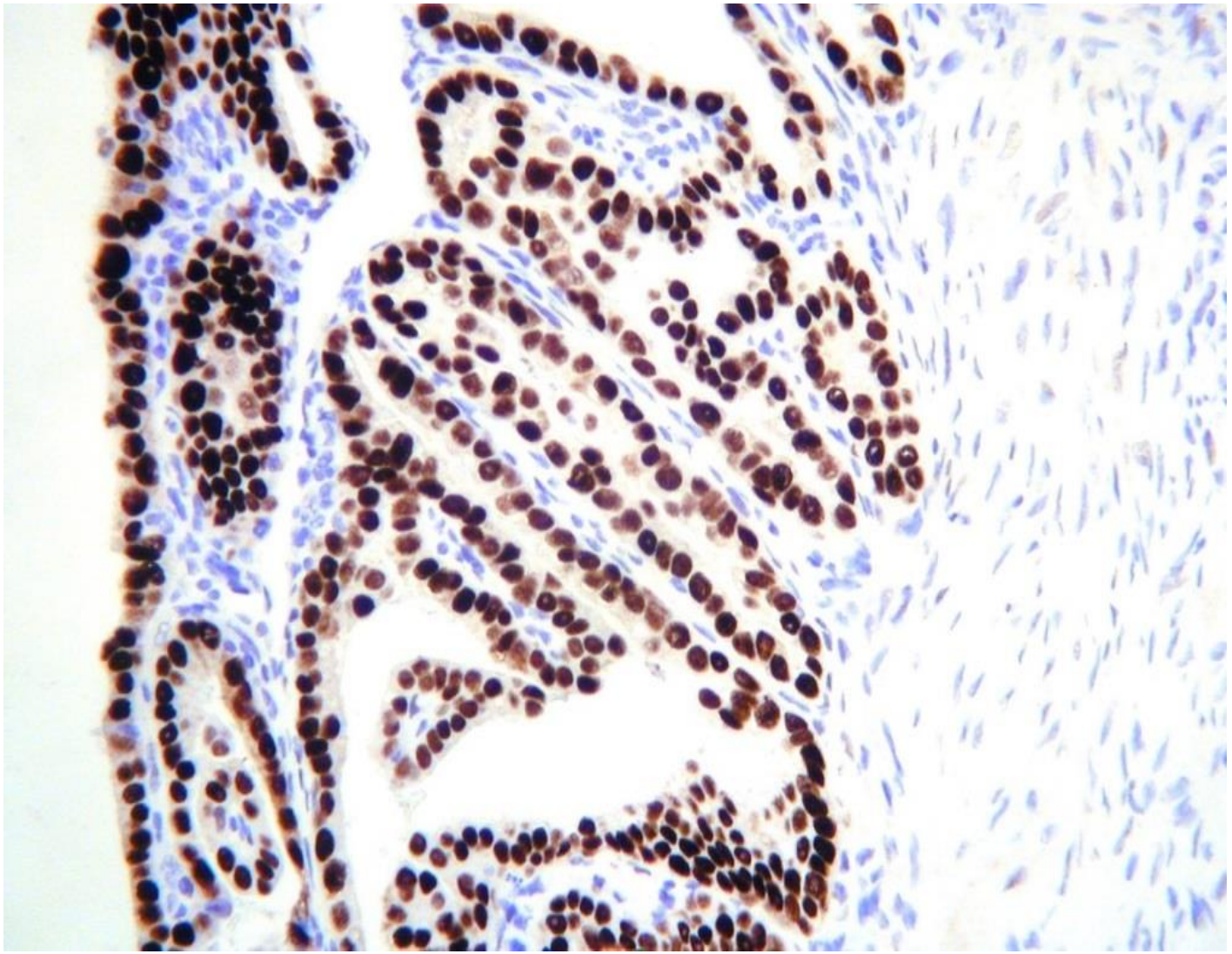
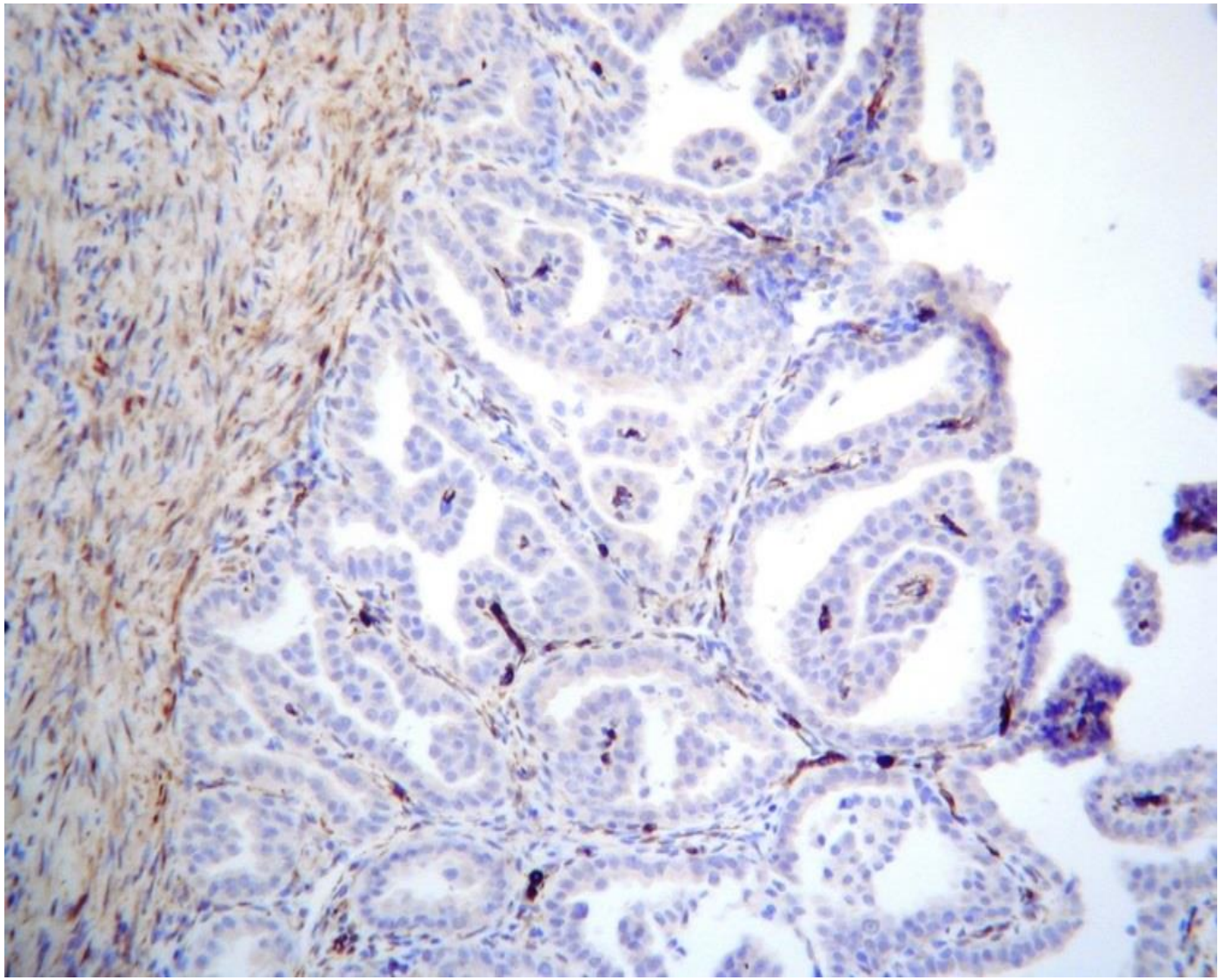


p53

USC INVOLVING FALLOPIAN TUBE



WT1

RESULTS

- tubal tumour considered to represent metastatic endometrial serous carcinoma in 26/32 cases
- considered to most likely represent metastatic endometrial serous carcinoma in 2/32 cases
- considered to independent tubal primary tumour in 3/32 cases
- considered of undetermined origin in 1/32 cases

RESULTS

- STIC-like lesion considered to be metastatic endometrial serous carcinoma in 12/17 cases
- considered most likely to be metastatic endometrial serous carcinoma in 2/17 cases
- considered to represent an independent tubal primary in 2/17 cases
- considered to be of uncertain origin in 1/17 cases

CONCLUSIONS

- Endometrial serous carcinoma shows tubal involvement in 20% when SEE-FIM protocol used
- 50% of tubal manifestations with STIC-like features
- 25% of tubal manifestations consist of STIC-like lesion only
- STIC-like lesions represent tubal metastases of endometrial serous carcinoma in most cases
- SEE-FIM protocol recommended on endometrial serous carcinoma apparently confined to the uterus (upstages significant percentage of cases)
- ? Is microscopic involvement of clinical significance