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Reliability of the methods for early diagnosis of carcinoma of the uterine cervix

by

G. F. MOSCOLO and G. G. NOVELLI

For the discovery of carcinoma of the cervix, which is the most common site of cancer of the female genital tract (4 out of 5 cases) and which constitutes the most common form of cancer when women alone are considered, we traditionally rely upon colposcopic and colpocytological examination, supported by histological studies if the results of these tests are positive.

The present report aims at a critical assessment of the work of the Centre for Colposcopy and Citology of the Second Obstetric and Gynaecological Clinic of the University of Padua, from its beginning (23-2-1970) to 31-5-1974. The advantages and limitations of each of the methods used are outlined.

1) *Colposcopy*

Advantages: a) changes in the exocervical epithelium, which are not obvious to the naked eye, can be differentiated with greater accuracy; b) a colposcopically benign lesion obviates the need for further tests, and in particular for a biopsy; c) precancerous or malignant epithelial atypia alerts the investigator early and necessitates a biopsy, thus leading to early and adequate treatment; consequently the finding of a suspected and non-positive lesion in case of cancer

From the 2nd Obstetric and Gynecological Clinic, University of Padua.

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should be considered an example of diagnostic reliability; d) the possibility of carrying out cytological tests or a surface biopsy ([1]).

Limitations: a) in pregnancy the cervix may simulate an exophytic appearance especially in cases of superimposed inflammation; b) apart from pregnancy, a pseudo-exophytic appearance may also be produced by heavy specific or non-specific (*E. coli*) bacterial colonisation; c) visualisation of the junction zone between the malpighian and the cylindrical epithelium, the preferred site for the initial development of malignant lesions, may present some problems, particularly in menopausal women where this area has moved to the inside of the cervical canal because of atrophy and involution. The proportion of intracervical cancers invisible by colposcopy is of some pratical significance, therefore. The number reported in the literature varies considerably, from 2.6% ([2]) to 57.2% ([3]). This divergence is probably due to differences in definition. Some investigators include epitheliomatous nodules surrounded by glands of the endocervical type in intracervical cancer; Held ([2]), however, limits the definition of intracervical cancer to neoplasia located in the depth of the cervical canal and therefore invisible in colposcopy.

2) *Colpocytology*

Advantages: a) In contrast to biopsy, it allows the removal of an extensive sample from the entire surface of the exocervix and endocervix, and in particular from the junction zone along its whole length; b) removal of the sample is entirely atraumatic and easy to carry out; c) a further sample may be taken even shortly after the initial one without altering the appearance of the mucosa and the desquamation characteristics.

Limitations: a) False positive results are produced by inflammatory lesions, particularly if the mucosa tested is atrophic, or if there is especially active regeneration in the area of metaplasia; b) False negative results (only a true limitation in relation to oncological identification) produced by intra-epithelial neoplasias which do not desquamate if masked, for example, by an area of thick leucoplakia; by invasive necrotic forms; occasionally by recurrence after radiotherapy; by preceding radical biopsy; by a technical error in the selection of the method and site for removal of the sample. In the literature the percentage of incorrect negative findings ranges from 3% ([4, 6]) to 16.7% ([5]).

3) *Histology*

Advantages: a) In contrast to colposcopic and colpocytological examination, the diagnosis obtained by histological methods is certain; b) the possibility of an architectural assessment of the epithelium facilitates the diagnosis of the initial invasiveness.

Limitation: a) Possible lack of precision in the findings because of the limited nature of the material under examination, both in extent and in depth; b) the sample is not « really » representative; c) technical problems, such as incorrect orientation of the sample section; d) difficulties in interpretation, as for example the distinction between severe dysplasia and carcinoma in situ.

We see from the above that the greatest diagnostic reliability is obtained from the use, and the agreement, of several tests. Thus, although cytology alone

can represent a valid mass screening method, it is certainly not possible to expect it to yield a definitive diagnosis, or to rely on it as the only method in cases with suspicious symptoms or clinical findings.

CASE MATERIAL

Our patient group consisted of 138 selected cases with suspected or established cancer of the cervix, on the basis of evidence found at screening. These were women who: 1) had been examined at the Centre for Colposcopy and Colpocytology of the Clinic; 2) had been admitted to our Institute for histological tests, clinical assessment and suitable treatment.

The final clinical-surgical assessment, supported by the histological evidence, which we regarded as the decisive criterion, is shown in Table 1. All the

Table. 1. *Clinical subdivision of our case material*

Stage 0	18 cases
Stage 1	55 cases
Stage 2a	16 cases
Stage 2b	18 cases
Stage 3	13 cases
Stage 4	12 cases
Exclusion of neoplastic lesions	6 cases
Total	138 cases

carcinomas were of the squamous type, except for two cases of adenocarcinoma at the site of ectopia, one case of exocervical and endocervical metastasis of adenocarcinoma of the endometrium, and of one case of persistence of adenocarcinoma of the cervical canal on the cupula.

Total agreement between the cyto-colposcopical and histological findings was found in 55 cases (41.3%); 10 of these were in stage 1, 2 in stage 2 a, 12 in stage 2 b, 2 in stage 3 and 2 in stage 4 (colposcopy was not undertaken in 5 cases).

This low percentage is due to the fact that positive colposcopic results are only obtained in pictures of carcinogenic exophytis or endophytis (not very frequent findings). If, however, we also include suspicious colposcopic pictures (see Table 2), in the light of the above considerations the various methods

Table 2. *Doubtful colposcopic pictures*

Raised leucoplakia	5
Raised mosaic	5
Leucoplakia base	3
Papillary base	5
Atypical reconstruction	7
True erosion	24
Non-characterised red area	1
Total	50

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show complete reliability in 74.4%. If we consider the various methods separately, the diagnostic reliability of cytology is 93.4% and that of colposcopy 88.7%.

Histological examination of surface biopsy samples shows 95.0% reliability, and when taken together with the cytological examination its diagnostic reliability is 100%.

Our patient group included three cases of suspect cytological response (class III, Papanicolaou). The colposcopic findings were also doubtful in these cases (true erosion, associated in one case with an atypical reconstruction zone, in the second case with mosaic, and in the third with leucoplakia). Surface biopsy, carried out by colposcopy, yielded positive histological findings. The surface biopsy sample (by colposcopy) yielded incorrect negative histological results in 13 cases; six of these patients had undergone biopsy before examination by us. The cytological examination carried out by us shortly after the first biopsy yielded positive results because of the residual presence of exfoliative cells around the primary lesion.

In two of these cases the colposcopic findings were negative, in three cases doubtful and in one positive. In five cases positive histological findings were obtained after repetition of the biopsy; in three of these cases the cytological findings were positive and the colposcopic findings doubtful, in one case both colposcopic and cytological findings were doubtful and in the last case the colposcopic findings were not noted and the cytology was positive.

RELIABILITY OF THE DIAGNOSIS OF DIFFUSION

In 17 of the 18 cases of intra-epithelial carcinoma a histological diagnosis had been obtained preoperatively (see Table 3). Of these, 10 had been obtained

Table 3. *Lack of agreement in the diagnosis of diffusion. Carcinoma in situ (CIS)*

Clinical stage	Preoperative histology	Operative histology	Colposcopy	Cytology	N. cases
1) Stage 0	CIS	CIS	suspected	positive	4
2) Stage 0	»	»	»	CIS	4
3) Stage 0	»	»	negative	positive	1
4) Stage 0	»	negative	»	»	1
5) Stage 0	»	»	»	CIS	1
6) Stage 0	»	»	not undertaken	»	1
7) Stage 0	»	CIS	negative	»	3
8 Stage 0	»	»	suspected	negative	2
9) Stage 0	negative	»	»	positive	1

by surface biopsy of colposcopically suspect lesions (true erosion in four cases, leucoplakia and mosaic in four and atypical reconstruction in the remaining two), and seven by quadrant biopsy (cases with negative colposcopic findings) based on a cytological diagnosis of carcinoma in situ. In the last case, where colposcopy revealed leucoplakia, mosaic and class IV cytology, the preoperative

histological diagnosis was « severe dysplasia, inflammatory erosion and parakeratosis leucoplakia ». The diagnosis of cancer in situ was only obtained from the surgical fragment. Cytologically a correct diagnosis of pre-invasion was obtained in nine cases; in seven of these, cytological examination yelded positive results, but without specifiying the intra-epithelial type of the neoplasia. In the other two cases, however, the cytological test yielded incorrect negative results, produced by co-existent trichomoniasis in one, and by the fact that the preceding biopsy had probably removed the lesion in the other.

Finally, in three cases the preoperative diagnosis of carcinoma in situ was not confirmed by examination of the biopsy fragment, which did not exhibit neoplastic lesions in the histological studies.

In 14 cases of invasive cancer a preoperative histological diagnosis of intra-epithelial carcinoma was obtained (see Table 4); in 10 of these the histological

Table 4. *Lack of agreement in the diagnosis of diffusion. Invasive carcinoma (CIN)*

Clinical stage	Preoperative histology	Operative histology	Colposcopy	Cytology	N. cases
1) Stage 1	CIS	CIN	positive	positive	1
2) Stage 1	»	»	suspected	»	5
3) Stage 1	»	»	positive	CIS	1
4) Stage 2	»	»	suspected	»	2
5) Stage 1	»	»	»	suspected	1
6) Stage 1	»	CIS	»	positive	3
7) Stage 1	CIN	negative	»	»	1
8) Stage 1	»	CIS	positive	»	2
9) Stage 1	»	CIN	negative	CIS	1
10) Stage 2 b	»	CIS	suspected	positive	1
11) Stage 4	CIS	explorative laparotomy	»	»	1

examination of the surgical fragment showed the invasive nature of the lesion; in three (No. 6), although the histological examination confirmed the intra-epithelial nature of the neoplasia, the clinical findings showed the diffusion to be in stage I; in another case (No. 11) explorative laparotomy revealed stage IV diffusion.

Except for one case (No. 5) where the cytological findings were doubtful, all these lesions were cytologically classified as IV or V (disease form with undifferentiated elements); in only three cases (No. 3, 4) was the intra-epithelial form diagnosed. Colposcopy yielded positive results in two cases (No. 1, 3) and doubtful results in the other 12. In addition, in three cases (No. 8, 10) where surgery was undertaken on the basis of a histological diagnosis of carcinoma in situ with initial infiltration, histological examination of the surgical fragment only showed « carcinoma in situ with aspects of glandular pseudo-invasion ». In all three cases cytology had diagnosed an invasive form; in two, classified as being in the first clinical stage, colposcopic findings were also positive; in the third case, classified as being in stage 2 b, colposcopy revealed raised leucoplakia. In another case

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with negative colposcopic findings (No. 9), the cytological diagnosis was an intra-epithelial form, whereas histological tests, both preoperatively and on the surgical fragment, showed an invasive form.

Finally, in one case (No. 7) where the cytological diagnosis was a form with barely differentiated elements, preoperative histological tests showed infiltration, whereas the surgical fragment was free from neoplastic lesions (sufficiently radical biopsy?).

DISCUSSION

Table 5 shows the cases where there was a substantial lack of agreement between the various methods. These were six cases of intra-epithelial carcinoma, four cases in stage 1, three cases in stage 2 and six cases of incorrect positive cytological findings.

Table 5. *Lack of agreement in the diagnosis of malignancy*

Patient	*Colposcopy*	*Cytology*
1. ML	Smooth leucoplakia - reg. mosaic - vaginitis	Cl II Trichomoniasis - reg. Displ.
2. MG	ectopia - remote reconstruction area - small remote smooth leucoplakia	Cl II
3. VN	remote reconstruction zone	Cl IV-CIS
4. UDE	not reported	Cl IV-CIS
5. DM	remote reconstruction zone	Cl IV-DA
6. MP	remote reconstruction zone - biopsy findings	Cl IV
7. CC	Ectopia - recent biopsy findings - vaginitis	Cl IV - severe dyskaryosis - appearance of culture cells
8. PA	remote reconstruction area - cc blood - biopsy findings	Cl IV - form with barely differentiated elements
9. TL	Leucoplakia base	Cl IV
10. AS	Well epithelialised closed cupula	Cl V - form with differentiated elements
11. CL	Ectopia - remote reconstruction zone - two areas of smooth leucoplakia	Cl II
12. PA	Dystrophic uterine cervix	Cl IV - form with barely differentiated elements
13. FL	remote reconstruction area - raised leucoplakia - signs of lacerations	Cl IV - CIN
14. LA	Ectopia - remote reconstruction area	Cl IV - CIS+CIN
15. ZM	remote reconstruction area	Cl IV - severe dyskaryosis
16. TG	Atypical reconstruction area - area of raised leukoplakia - Dysplasic scar on 1.a. - colpitis	Cl IV - pavement form with little differentiation
17. PM	Ectopia - reconstruction area with atypical vascularisation	Cl IV - form with barely differentiated elements (subsequently: severe dyskaryosis)
18. ME	Original mucosa	Cl IV - atrophic menopause, large bare nuclei
19. BM	Ectopia with advanced reconstruction area. Irregular mosaic, hence vaginitis	Intense trichomoniasis; subsequently: CIS

Stage 0

In two cases cytology yielded an incorrect negative result (in one case three severely diskaryotic elements of the type found in cancer in situ were revealed, but were interpreted as the expession of the intense trichomoniasis which was present); in three cases cytology yielded diagnostic agreement (class IV, cancer in situ), and in the remaining case class IV without specification. Colposcopy yielded doubtful results in two cases, negative results in three, and in one case the findings were not noted.

Stage 1

In three of these cases the preoperative histological examination yielded negative results; these patients had undergone biopsy in another diagnostic centre

Histology	*Clinical stage*
CIS over a very limited area (ser. ex. neg.)	Stage 0
CIS - chronic cervicitis	Stage 0
Circumscribed carcinomatous alterations of the surface epithelium	Stage 0
CIS (after 2 biopsies - negative fragment)	Stage 0
Very limited area of lining epithelium with crowded dysmorphic cells (strongly suspect)	Stage 0
CIS over a very limited area	Stage 0
Chronic inflammation (prev. ex.: CIS)	Stage 1
Haemorrhagic necrotic material with pavement epithelium phenom. of regression (prev: CIS+CIN)	Stage 1
Acanthosis and parakeratosis prev. ex: CIS	Stage 1
CIS + CIN	Stage 1
Chronic cervicitis with papillary features and signs of severe dysplasia	Stage 2a
Cancer of the cervix with barely differentiated elements	Stage 2a
CIS + possible ne. infiltrations (fragment: severe dysplasia)	Stage 2b
Chronic cervicitis	negative
Chronic cervicitis	»
Chronic papillary cervicitis (3 biopsies)	»
Chronic cervicitis (4 biopsies)	»
Hyperplasia of the lining epithelium	»
Severe dysplasia	»

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previously, where the diagnosis was carcinoma in situ in two cases and circumscribed infiltration in the third (these cases had been examined previosly); in the fourth case the histological findings were positive. Cytology yielded positive results in all four cases. Colposcopy yielded doubtful findings in one case and negative findings in three; of the latter, two retained signs of the preceding biopsy which, as we had anticipated, had entirely removed the lesion.

Stage 2

In one case histological results were positive, although at the doubtful limit, while the cytological findings were incorrectly negative and the colposcopic results doubtful. In the second case the only divergent element was colposcopy, which only revealed a « dystrophic uterine cervix ». In the third case, cytologically classified as invasive (colposcopy revealed raised leucoplakia), biopsy showed carcinoma in situ with possible initial infiltration, whereas the surgical fragment was free from neoplastic lesions and only showed severe dysplasia.

Incorrect positive cytological findings

Of six cases with incorrect positive cytological findings, histological tests showed chronic cervicitis in four, hyperplasia of the lining epithelium in one, and severe dysplasia in one. In three cases colposcopy yielded negative findings, results, in one case (No. 18) there was atrophic menopausal epithelium with large and in three cases doubtful findings. As to the incorrect positive cytological bare nuclei persisting after anti-inflammatory and estrogenic therapy. In another case (No. 19) where diskaryosis had been attributed to intense trichomoniasis, its persistence after specific anti-inflammatory treatment had suggested an intraepithelial form, which was negated by the histological results, however. It should be stressed that a large number of these cases have undergone repeated periodical histological check-ups since then, with negative results.

CONCLUSIONS

A critical assessment of our case material suggests the following thoughts:

1) Incorrect negative colposcopy: 15 cases (11.2%).

In three of these the preceding biopsy presumably removed the entire lesion.

2) Incorrect positive colposcopy: none.

3) Incorrect negative cytology: 3 cases (2.1%).

In two cases carcinoma in situ was confirmed histologically; in the third case histological confirmation of the dysplastic nature of the lesion had been obtained at the outset, although this finding had been at the limit of the positive. If we also include the six cases of incorrect positive results (4.2%) we obtain a percentage of error of 6.3%. The diagnostic reliability of colposcopy and colpocytology, taken separately, is therefore at the middle of the published values.

4) Incorrect negative histological findings: 13 cases (9.4%).

Of these, six had undergone previous biopsy, resulting in a diagnosis of cancer in situ in three cases, and circumscribed infiltration in the other three (sufficiently radical biopsy). in four cases positive findings were obtained after a second biopsy, in one case after a third biopsy, and in the other two cases only the surgical fragment yielded positive findings.

5) Cytology showed better diagnostic reliability than histology in the diagnosis of invasiveness (14 incorrect histological results in situ, as compared to three cytological results).

This is due to the large size of the area from which the cytological sample is taken, in comparison with a surface biopsy, so that the histologist cannot exclude the possibility of infiltrations in areas close to the site of biopsy.

However, histology is more reliable than cytology for the diagnosis of pre-invasiveness (17 of 18 cases by histology; nine of 18 cases by cytology). This is readily understood if we consider the often hard to define and uncertain cellular features which characterise cancer in situ cytologically, in comparison with the reliability of histological examination, which allows architectural assessment of the epithelium.

6) *We are convinced that there are cases of active cancer wih have been incorrectly labelled as positive cytologically, as they have not been confirmed by histological tests.* Indeed, we found that when the histological tests were repeated over a period, and if we were fortunate in our choice of samples for biopsy, histological confirmation of the neoplasia was sometimes possible. In other cases examination of the surgical fragment after surgery for various indications confirmed the suspicion expressed by the cytologist. *To avoid these errors and delays in diagnosis, in cases of positive cytological findings and negative histological findings we think it advisable to undertake conisation of the uterine cervix and to undertake a serial section of the fragment, with an adequate number of sections.* This would allow a reliable diagnosis by means of a small intervention which does not affect the subsequent fertility of the patient, and which also represents a definite therapeutic measure in case of pre-invasive cancer.

SUMMARY

The authors compare the reliability of various methods for early diagnosis in a selected patient group of 138 women with cancer of the cervix or suspected of such on the basis of screening. For the diagnosis of malignancy, cytology was reliable in 93.4%, colposcopy in 88.7% and histological examination of surface biopsy material in 95.0%. Cytology plus histology showed 100% reliability. In regard to diffusion of the neoplasia, cytology was found to be more reliable for the diagnosis of invasiveness, and histology more reliable for the diagnosis of pre-invasiveness. In cases where the results of the various methods are not in agreement, the authors propose the use of conisation.

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