

(いわゆる平坦型コンジローマ)であり、腫瘍 (CIN 1) とよぶことは科学的な観点から正しいとはいえないため、両者を区別するべきであると考えられる病理医が少なくない。しかし、①組織像のみで両者を鑑別することは必ずしも容易ではなく、診断者間の再現性が低いと考えられること、②両者ともにほとんどが自然消退し、高度病変に進展するリスクが低いこと、鑑別することに臨床的意義がほとんどないこと、などの理由から LAST ガイドライン (2012 年) では両者をあわせて LSIL とすることが推奨されるに至った。WHO 分類 (2014 年) ではこの考え方が反映され、LSIL は HPV 感染による病変として厳密に定義されることになった一方で、CIN 1 が依然としてその同義語として記載されている。すなわち、LSIL という一つの診断カテゴリーの中に、① HPV 感染、② 腫瘍 neoplasia (CIN 1)、という 2 つの異なる病態が含まれている。これらを正確に区別することが理想的だが、現時点ではそれを可能とする有効な補助的手段がなく、今後解決されるべき課題の一つとなっている。ただし、実地臨床においては LSIL の亜分類よりも、これらを反応性異型や HSIL と区別することの方がより重要である。

外向性の乳頭状増殖によって特徴づけられる尖圭コンジローマ condyloma acuminatum の多くは外陰部で発生し、子宮頸部では比較的稀な病変である。尖圭コンジローマも LSIL に含まれるが、6 型、11 型などのローリスク HPV によって生じ、扁平上皮癌に進展することは基本的にはない (33 頁参照)。したがって、尖圭コンジローマとの混乱を防ぐため、ほとんどがハイリスク HPV によって生じる平坦な LSIL に対して平坦型コンジローマという名称を用いることは避けた方がよい。

表 1 扁平上皮癌の前駆病変の分類

	軽度異形成	中等度異形成	高度異形成	上皮内癌	異形成/上皮内癌分類
	CIN 1	CIN 2	CIN 3		CIN 分類
コンジローマ	CIN 1	CIN 2	CIN 3		コンジローマ/CIN 分類
	CIN 1	CIN 2	CIN 3		子宮頸癌取扱い規約 第 2 版 (1997 年), 第 3 版 (2012 年)
	LSIL (細胞診)	HSIL (細胞診)			ベセスダ分類 (1989 年)
	LSIL (組織診)	HSIL (組織診)			WHO 分類 (2014 年)

扁平上皮癌は軽度異形成から中等度異形成、高度異形成に段階的に進展し、上皮内癌を経て発生すると考えられていた。しかし、Richart らによって提唱された子宮頸部上皮内腫瘍 cervical intraepithelial neoplasia (CIN) 分類 (1969 年) では、高度異形成と上皮内癌が、①判別の再現性が高くない、②しばしば併存する、③浸潤癌に進展するリスクが同程度で、臨床的取扱いも同様である、などの理由からともに CIN 3 に分類された。その後、コンジローマと CIN はいずれもコイロサイトーシスを示すことから、一連の病変として位置づけられるようになった。本邦の『子宮頸癌取扱い規約』第 2 版 (1997 年)、第 3 版 (2012 年) は WHO 分類 (1994 年) にしたがってコンジローマを CIN 1 とみなしてきた。細胞診の報告様式のガイドラインであるベセスダシステム (1989 年) で用いられてきた LSIL、HSIL が WHO 分類 (2014 年) では組織診断用語として採用されたが、この場合の LSIL は細胞診判定用語としての LSIL とは完全に対応するものではない。すなわち、WHO 分類 (2014 年) では LSIL が HPV 感染として位置づけられ、基底側において高度の核異型や異型核分裂が認められないものと規定されている。したがって、従来の CIN 1 の中には HSIL に相当するものが含まれていると考えられる。

臨床事項

20 代前半に多い。特徴的な臨床症状はない。細胞診を契機としてコルポスコ



a) 軽度異形成 **mild dysplasia (CIN1)**^(註2)

異形成が上皮の下層 1/3 に限局する扁平上皮内病変である。

コイロサイトーシスが上皮の表層 1/3 にあれば、本規約では軽度異形成に入れる。この HPV 感染による細胞異型であるコイロサイトーシスは、異形成の診断に見逃してはならない重要な所見である。大きくて、クロマチンに富み、しわが寄った核が、淡明な細胞質と厚い細胞膜をもった大きな細胞にみられるのが特徴的である。さらに、二核や多核の淡明細胞があれば、診断に役立つ。コイロサイトーシスは、細胞形態の記載であり診断用語としては用いず、所見として附記する。ただし、コイロサイトーシスを認めても尖形コンジローマは本項には入れない。

b) 中等度異形成 **moderate dysplasia (CIN2)**

異形成が上皮の下層 2/3 にある扁平上皮内病変である^(註3)。

c) 高度異形成 **severe dysplasia (CIN3)**

異形成が上皮の表層 1/3 に及ぶ扁平上皮内病変である^(註4)。

上皮の層形成や極性の乱れは著しいが、完全には失われていない。

d) 上皮内癌 **carcinoma in situ (CIN3)**

癌としての形態学的特徴をもつ細胞が上皮の全層におよぶ扁平上皮内病変である。

上皮内癌には、表層に角化層あるいは乾燥した薄い層がみられることがある。本病変にはしばしば腺侵襲 *gland involvement* を伴うが、これは浸潤とはしない。

[注 1] 婦人科細胞診の新しい記載法であるベセスダ方式 The Bethesda System では、従来用いられてきた上皮内病変の記載方式である異形成-上皮内癌 (CIN) 分類を扁平上皮内病変 *squamous intraepithelial lesions* とし、軽度扁平上皮内病変 *low grade squamous intraepithelial lesion (LSIL)* と高度扁平上皮内病変 *high grade squamous intraepithelial lesion (HSIL)* の 2 つに分類する。HPV に特徴的な細胞の変化、軽度異形成、および両者の共存は、軽度扁平上皮内病変とする。中等度異形成、高度異形成-上皮内癌 (CIN2 and 3) は高度扁平上皮内病変とする。

[注 2] 本規約では HPV 感染による細胞異型であるコイロサイトーシスが軽度異形成に含まれるため、軽度異形成の範囲が前規約より広がる。

[注 3] 核異型を示す細胞は上皮の下層 1/3 に限局するが、核異型が高度な場合は中等度異形成に入れるとする意見もある。

[注 4] 核異型を示す細胞は上皮の下および中 1/3 にしかないが、核異型が高度な場合は高度異形成に入れるとする意見もある。

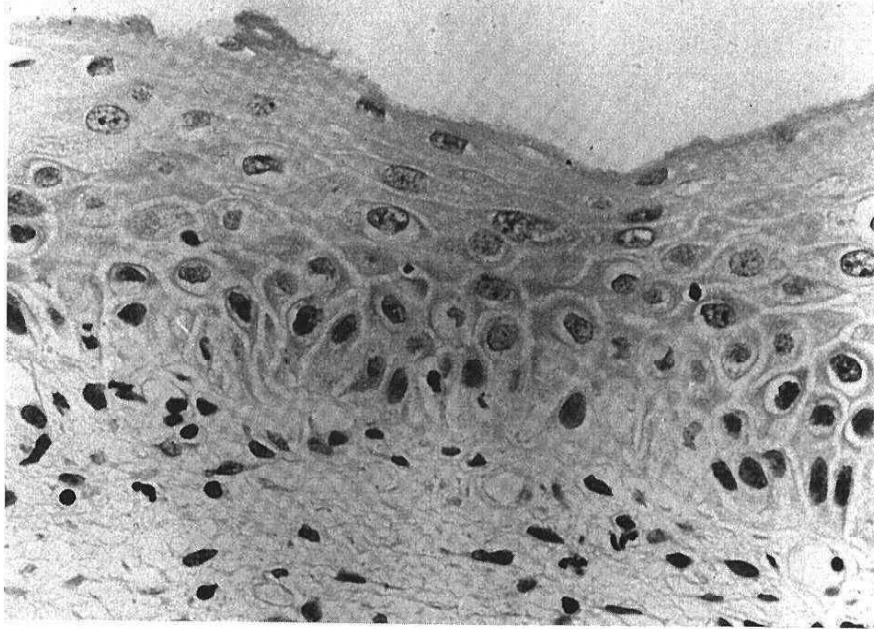


Fig. 7.25 Basal abnormalities of uncertain significance (BAUS). The basal layers show minor nuclear atypia. $\times 540$.

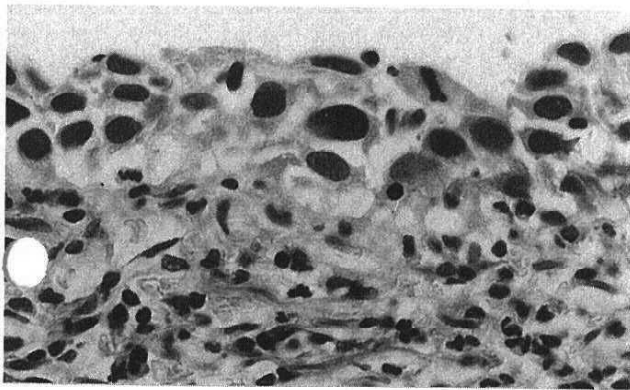


Fig. 7.26 CIN (grade not specified). Although the nuclei show marked atypia, the epithelium is thin and the architecture is distorted, so grading is not possible. $\times 550$.

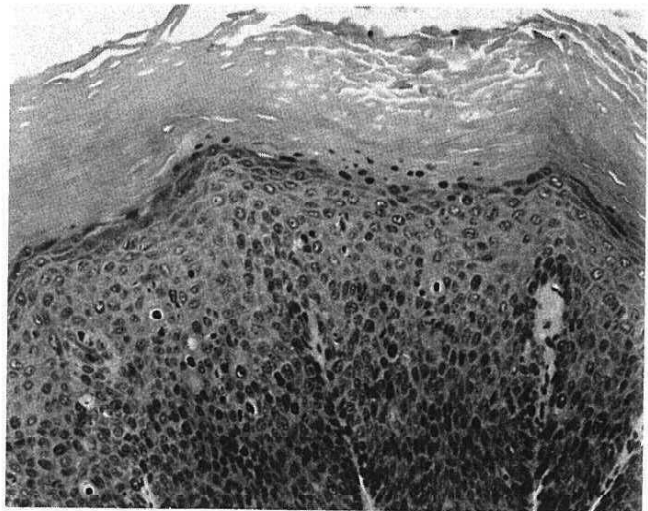


Fig. 7.27 CIN 3, showing marked hyperkeratosis and a granular layer. $\times 190$.

in the clinical and colposcopic appearances of leucoplakia (Fig. 7.28) and tends to occur towards the ectocervical extreme of the transformation zone whereas the small cell type is more usually found in the part of the transformation zone which is in the cervical canal.

Cervical intraepithelial neoplasia affects both the surface and the crypts. Anderson & Hartley (1980) studied 343 cervical conization specimens containing CIN 3 and found that 88.6% showed some involvement of the crypts by CIN. The mean depth of involvement was 1.24 mm and the maximum was 5.22 mm. 99.7% of the population are included in the mean plus three standard deviations, and this figure was 3.8 mm. It is essential that this amount of crypt involvement is taken into consideration when

CIN is being treated, particularly when local destructive techniques are being employed, otherwise there is a danger that viable CIN may be left in the depths of the crypts and covered by regenerating stroma and epithelium, perhaps to develop occultly into an invasive carcinoma. Abdul-Karim et al (1982) compared the depth of crypt involvement in the three grades of CIN and found, not surprisingly, that the less severe grades involved the crypts less deeply. The mean, plus three standard deviations for CIN 1, CIN 2 and CIN 3 were 1.26 mm, 3.06 mm and 4.80 mm respectively. Furthermore, Abdul-Karim



Fig. 7.28 Colposcopic photograph of the cervix from which the biopsy shown in Figure 7.27 was taken. The entire posterior lip of the cervix is covered by opaque, white keratin, giving the naked-eye and colposcopic appearances of leucoplakia. $\times 5$.

et al (1982) found that the more severe forms of CIN occupied a greater linear dimension on the surface of the cervix and that the depth of crypt involvement and linear dimension all increased with increasing age of the patient for the same degree of CIN.

MICROINVASIVE CARCINOMA

The concept of microinvasive carcinoma was introduced by Mestwerdt as long ago as 1947 to apply to lesions which did not extend more than 5 mm into the stroma, in the belief that these small lesions had a much better prognosis than the rest of the stage I lesions (Mestwerdt 1951). This difference in prognosis is the most crucial point in the deliberations over early invasive carcinoma of the cervix; can early invasive carcinoma be treated in a relatively conservative fashion and, if so, is it possible to define histologically the point in the growth of the tumour at which radical treatment becomes necessary? The ideal definition of microinvasive carcinoma should reflect this therapeutic approach.

Burghardt (1982) suggests that the course of the development of cervical cancer has three latency periods. The first is between the appearance of intraepithelial atypia and the first invasive breakthrough into the stroma. A second latency period exists between this very first breaching of the basement membrane and the formation of recognizable buds of propagating invasive tumour.

The very small but recognizable tumour then has to take on certain qualities and reach a certain size before it can overcome the body's local defence mechanisms and establish itself as a dominant, progressive carcinoma capable of metastasis. This is the third latency period and it is when the tumour has reached the end of this stage

that it ceases to be a microinvasive carcinoma. In other words, a diagnosis of microinvasive carcinoma should indicate a tumour which, although being of measurable size and locally invasive, has a negligible potential for metastasizing.

Histology of early invasive growth

The earliest recognizable stage of stromal invasion is shown in Figure 7.29 where there is a well-defined small bud of invasive cells, with similar morphology to the CIN 3 from which it has arisen. As the invasion advances slightly, other morphological features may become apparent. Frequently, the invasive tongues may appear better differentiated than the matrix CIN (Fig. 7.30). Whether this increased amount of cytoplasm with eosinophilia and

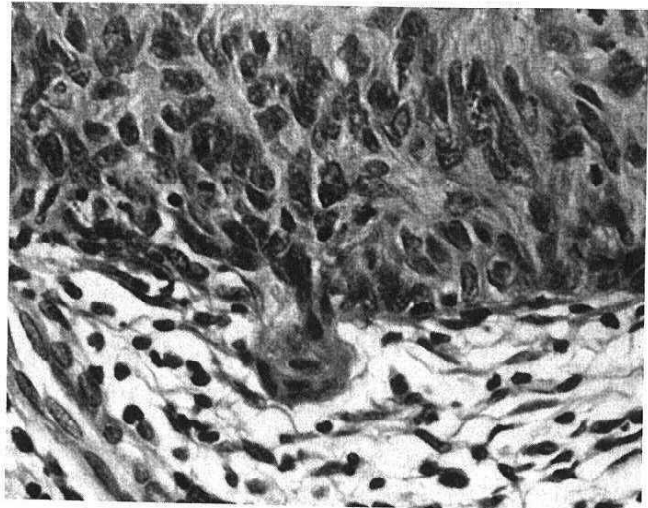


Fig. 7.29 Microinvasive carcinoma. Very early stromal invasion, with only a small bud of cells pushing into the stroma. $\times 620$.

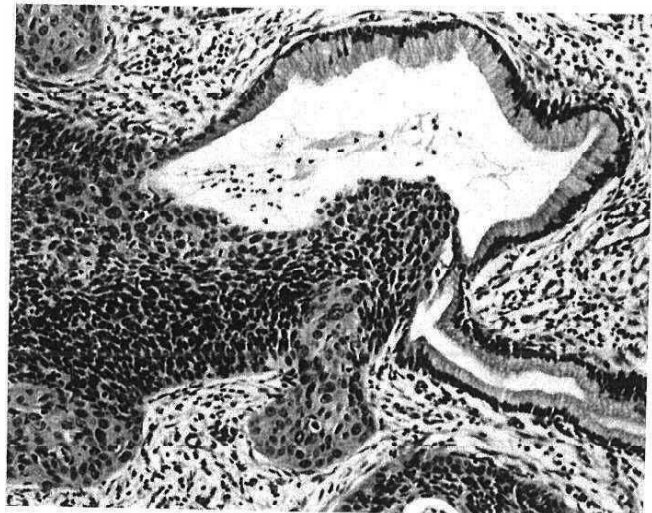


Fig. 7.30 Microinvasive carcinoma. The invasive buds appear to be better differentiated than the CIN from which they arise. $\times 155$.

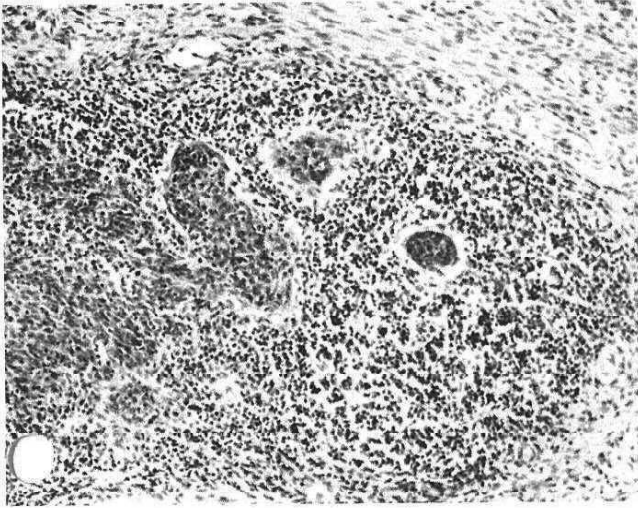


Fig. 7.31 Microinvasive carcinoma. A dense infiltrate of lymphocytes surrounds the invading tumour. $\times 155$.

nuclear clearing is genuine differentiation or degeneration is arguable (Lohe, 1978; Buckley et al, 1982). There is often a stromal reaction to the invasive tumour, which may be a dense, localized lymphocytic infiltrate (Fig. 7.31) or a loosening and apparent oedema of the stroma (Fig. 7.32); sometimes both these features are seen together. These three features — better differentiation of the invasive elements, clearing of the stroma and a lymphocytic infiltrate — are changes which can be helpful to the histopathologist in deciding whether early stromal invasion is present or not in ambiguous cases.

As the tumour becomes larger and progresses from the individual finger-like processes, seen in Figures 7.30, 7.31 (Fig. 7.32, to a more complex pattern, other morphological features must be taken into account. These are lymphatic channel involvement, the dimension of the tumour and the pattern of growth.

Lymphatic channel involvement

Permeation or invasion of endothelial-lined spaces, which may be either lymphatics or blood vessels, should always be looked for in invasive tumours. From first principles, it should seem reasonable to suggest that a tumour in which lymphatic channel involvement is present is more likely to have lymph node metastases and therefore to have a worse prognosis, necessitating more radical treatment. The information available on the relationship between lymphatic channel involvement and lymph node metastases in the cervix is conflicting and is hampered by the diversity of the cases diagnosed as microinvasive carcinoma. Roche & Norris (1975) examined the cervixes in 30 examples of microinvasive carcinoma, which included cases with invasion extending to between 2 and 5 mm from the surface epithelium. Using step-serial sections, they found

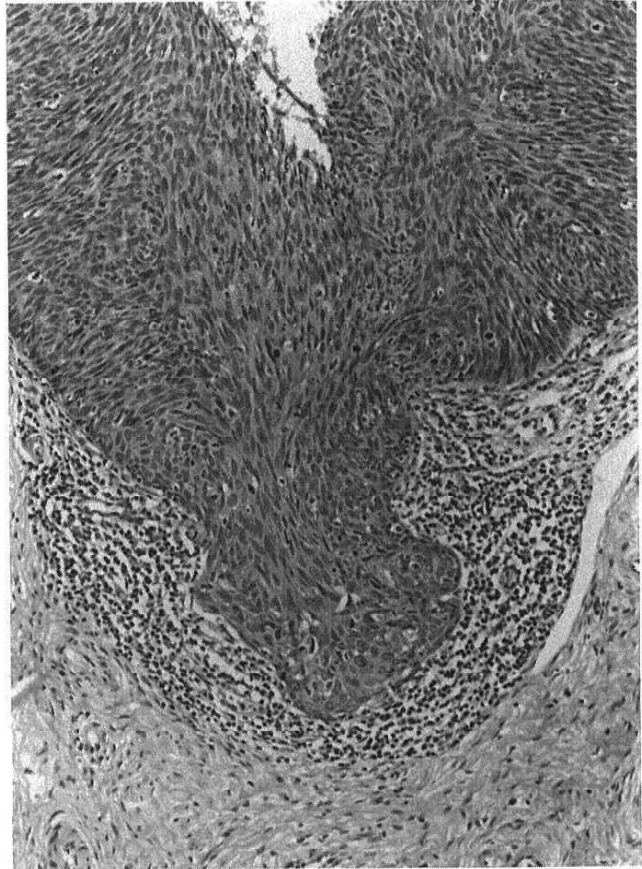


Fig. 7.32 Microinvasive carcinoma (early stromal invasion). The lymphocytic infiltrate is prominent around the invasive bud. $\times 138$.

‘capillary-like space’ involvement in 57% of patients, all of whom had been treated by radical hysterectomy including lymphadenectomy. Lymph node metastases were not found in any of the patients, suggesting that the finding of capillary-like space involvement does not mean an increased risk of lymph node metastases. However, subsequent figures from Burghardt (1982), Holzer (1982) and Kolstad et al (1982) suggest that the presence of lymphatic channel involvement does increase the risk of metastasis.

Although it is apparent that the chance of lymphatic channel involvement increases as the size of the tumour increases (Hasumi et al, 1980), this phenomenon may be observed in cases where the depth of invasion is less than 1 mm. This gives rise to a serious dilemma in recommending treatment; if it is believed that the presence of lymphatic channel involvement indicates a significant risk of lymph node metastases, then radical treatment should be carried out. Indeed, examples of widespread lymph node metastases occurring in women in whom the tumour invades to a depth of 1 mm or less have been reported (Hasumi et al, 1980; van Nagell et al, 1983; Collins et al, 1989) but this is a very rare phenomenon and the inci-

dence of lymph node metastases at a depth of invasion of 1 mm or less is practically zero. Even so, most pathologists and gynaecologists have reservations about treating any patient in whom true lymphatic channel involvement is seen by conization or simple hysterectomy. Further problems are encountered because of the difficulty in recognizing lymphatic channel involvement with certainty. If the tumour cells are surrounded by a regular space bounded by an endothelium (Fig. 7.33) there can be little doubt, but confusion can be caused by tissue shrinkage and tearing around a small invasive bud, which may give a false impression of a lymphatic channel or blood vessel.

Three dimensions

There is general acceptance of the fact that the deeper the tumour invades the worse the prognosis will be and the greater is the need for radical treatment. Burghardt (1982) took the evaluation of tumour size two stages further than a simple measurement of depth of invasion and suggested that the volume of invasive tumour gives the most reliable indication of prognosis. The cone biopsy is meticulously examined by step-serial sections, so that the distance between sections can be accurately estimated. Using this technique, not only can the tumour size be measured in two dimensions on the single section that shows the largest area but, by counting the number of sections showing the tumour and knowing the distance between sections, the third dimension can be calculated. The total volume of the tumour can thus be assessed. After experience with this method, Burghardt & Holzer (1977) concluded that there is no risk of metastatic spread up to a tumour size of 500 mm³, provided that no vascular invasion is seen. The same author (Burghardt, 1982) adds that the only fatal case of microinvasive carcinoma he has seen was in an example with widespread lymphatic

channel involvement, but with a tumour volume of less than 500 mm³. It has to be accepted, however, that this technique for measurement of volume cannot be employed in a busy routine laboratory. There is, on the other hand, no problem in measuring the tumour size in two dimensions in the section that shows the greatest area of tumour and it is recommended that this should be done, in preference to the single measurement of depth of invasion, particularly now that the International Federation for Gynecology and Obstetrics (FIGO) definitions of stage Ia1 and stage Ia2 include these two measurements. It is probable that the most significant ultimate factor is in fact the surface area of the advancing face of the invasive tumour, because this is the interface between the tumour and the 'host'; the larger this area, the more vascular channels will be encountered and the greater is the chance of metastases.

Growth pattern

The earliest microinvasive tumours have a finger-like pattern of growth, as shown in Figures 7.30, 7.31 and 7.32. As the tumour becomes larger, this pattern may change to produce a confluent growth (Fig. 7.34). Boyes et al (1970) first promoted the idea that confluent masses of neoplastic cells were more likely to be associated with metastatic spread. Unfortunately, yet again, this point is dogged by imprecise definitions; exactly what is meant by confluent growth is far from clear. It is probable that,

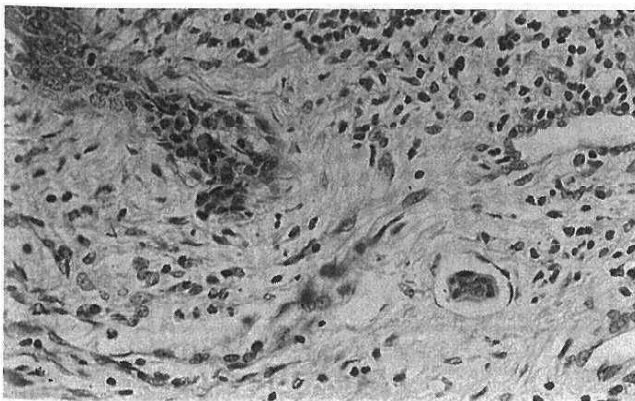


Fig. 7.33 Lymphatic channel involvement in microinvasive carcinoma. The endothelial lining of the vessel is clearly seen. $\times 245$.

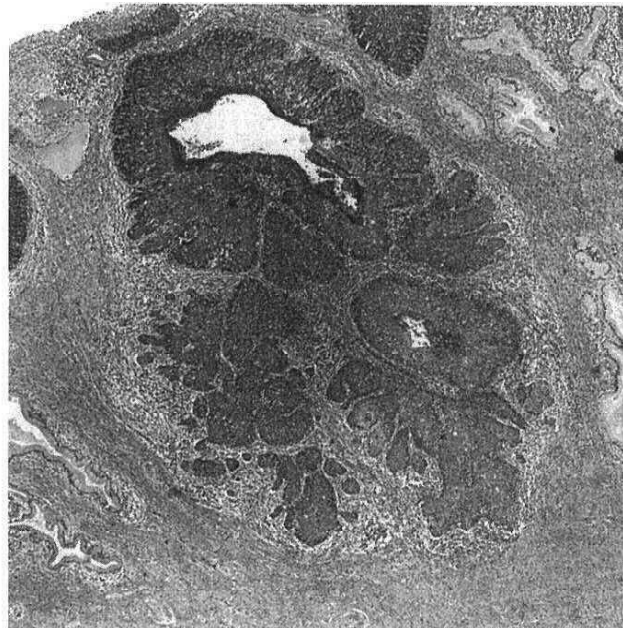


Fig. 7.34 Confluent pattern of invasion in microinvasive carcinoma. $\times 25$.

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by and large, the appearance of a so-called confluent pattern is related to tumour size; the larger microinvasive carcinomas nearly always present a confluent pattern. Roche & Norris (1975) found no association between confluent growth pattern and lymphatic channel involvement and doubt its significance in tumours invading no more than 5 mm.

The definition of microinvasive carcinoma

The search for a definition for microinvasive carcinoma is the quest for the histological criteria that will allow the reliable identification of the maximum disease that can safely be treated in a conservative fashion. Many definitions have been proposed over the years but it is generally the internationally accepted staging classification put forward by FIGO that is used. The previous definitions of microinvasive carcinoma used by FIGO have been imprecise and have not helped in management; the latest (1995) modification (Creasman, 1995) is shown in Table 7.1. This classification divides stage Ia (microinvasive) carcinoma into two categories, stage Ia1 and stage Ia2, both of which are defined by precise measurement. Stage Ia1 includes all lesions that invade up to 3 mm into the stroma and are not more than 7 mm wide. This category therefore embraces all the minimally invasive and unmeasurable lesions included in stage Ia1 in the previous (1985) classification as well as the smaller of the lesions that were previously included in stage Ia2. Stage Ia2 lesions are now defined as those that invade from 3 mm to 5 mm into the stroma and have a maximum width of

Table 7.1 1995 modification of FIGO staging of carcinoma of the cervix uteri (Creasman, 1995)

Stage	Description
Stage 0	Preinvasive carcinoma (CIN 3, carcinoma in situ)
Stage I	Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded)
Ia	Measured stromal invasion with maximum depth of 5 mm and no wider than 7 mm
Ia1	Measured invasion of stroma up to 3 mm in depth and no wider than 7 mm
Ia2	Measured invasion of stroma of 3-5 mm in depth and no wider than 7 mm
Ib	Clinical lesions confined to the cervix or preclinical lesions greater than stage Ia
Ib1	Clinical lesions no greater than 4 cm in size
Ib2	Clinical lesions greater than 4 cm in size
Stage II	Invasive carcinoma that extends beyond the cervix but has not reached either lateral pelvic wall; involvement of the vagina is limited to the upper two thirds
Stage III	Invasive carcinoma that extends to either lateral pelvic wall and/or the lower third of the vagina
Stage IV	Invasive carcinoma that involves urinary bladder and/or rectum or extends beyond the true pelvis

7 mm. Measuring the horizontal spread of the invasive tumour can cause problems if there is more than one focus of invasion. If this is the case, the lateral spread of each individual invasive lesion should be measured and the figures added together to give a total for horizontal spread.

It has already been emphasized that the value of recognizing microinvasive carcinoma is to define a group of early invasive carcinomas which have negligible risk of

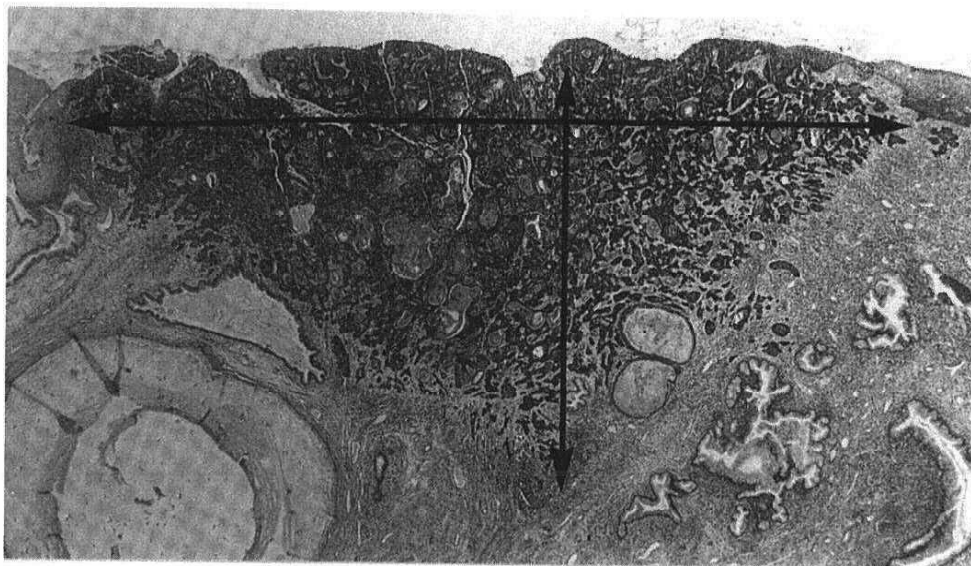


Fig. 7.35 Microinvasive carcinoma. Measurements in two dimensions are taken as shown. $\times 17$.

metastases and which, when adequately treated, do not recur. Since the publication of the previous (1985) FIGO staging for cervical cancer, there have been many reports retrospectively analysing the data from series of women with microinvasive carcinoma, most of whom were treated by radical hysterectomy, to determine how the classification of microinvasive carcinoma relates to outcome and whether or not it can be used to guide definitive treatment (Maiman et al, 1988; Ebeling et al, 1989; Kolstad, 1989; Tsukamoto et al, 1989; Greer et al, 1990; Burghardt et al, 1991; Sevin et al, 1992). It is generally agreed that stage Ia1 carcinoma (early stromal invasion) behaves in the same way as CIN and that conservative excisional methods of treatment can be used safely if 1 mm is taken as the upper limit for depth of invasion in this category. Stage Ia2, however, is a heterogeneous category, women with larger tumours within the defined measurements having a much higher risk of lymph node metastases and recurrence than those with smaller tumours. Pooled data has indicated that a maximum depth of invasion of 3 mm or less is associated with a risk of lymph node metastasis of only 0.3% and a risk of an invasive recurrence of 0.2%. On the other hand, invasion of 3.1–5.0 mm is associated with an overall risk of lymph node metastases of 7.4% and a recurrence rate of 5.4% (Sevin et al 1992). FIGO stage Ia must therefore **not** be taken as a definition of microinvasion that can be used to determine whether a patient should be treated conservatively or radically; many patients whose tumours fall within this category need radical treatment. All the available evidence indicates that the upper cut-off point for conservative treatment should be a maximum depth of invasion of 3 mm and that lymphatic channel involvement should be absent. Any lesion larger than this should be treated radically. The most recent (1995) FIGO definition takes this into account with the result that the division into stage Ia1 and stage Ia2 now more closely relates to treatment than was the case with previous schemes and, with the addition of a lateral measurement, is similar to that proposed by the Society of Gynecologic Oncologists in 1974 (Creasman et al, 1985) and the Japan Society of Obstetrics and Gynecology in 1978 (Noda et al, 1979).

Preclinical invasive carcinomas of the cervix with dimensions greater than those acceptable as stage Ia carcinoma have previously been referred to as 'occult' invasive carcinomas. This word has not been included in the current FIGO classification; these tumours should be designated by the histopathologist simply as stage Ib carcinomas.

The treatment of individual women with microinvasive carcinoma of the cervix must, of course, be determined by taking into account a number of factors, of which tumour size is only one, albeit often the most important. It is the responsibility of the histopathologist reporting preclinical

invasive squamous cell carcinoma of the cervix to record the following features:

1. The size of the invasive tumour in two dimensions in the section which shows the greatest area of the lesion (Fig. 7.35) (unless the invasion is peg-like early stromal invasion and is not measurable)
2. The presence or absence of lymphatic channel (capillary-like space) involvement
3. Whether the growth pattern is finger-like or confluent
4. Whether excision of the CIN and invasive elements is complete or not.

The accurate measurement of the size of the tumour means that a calibrated optic must be used in the microscope. Any report which does not include all the above information is incomplete and unsatisfactory. In addition, it may be useful to record how close the edge of the tumour is to the margins of the specimen, whether or not there is an inflammatory infiltrate surrounding the tumour and the histological type of the tumour cells.

TECHNICAL ASPECTS OF THE DIAGNOSIS OF PREMALIGNANT DISEASE

Colposcopy

Epithelial abnormalities of the cervix are initially picked up and diagnosed by exfoliative cytology, further evaluated by colposcopy and definitively diagnosed by histology. Full accounts of colposcopy are available elsewhere (Coppleson et al, 1978; Cartier, 1984; Burghardt, 1991; Anderson et al, 1992) but it is appropriate to present here a broad outline of the principles involved and to discuss briefly the important part that the colposcopic examination plays in the management of women with preclinical neoplasia of the cervix.

Colposcopy is a technique for the examination of the cervix using relatively low, stereoscopic magnification and bright illumination. Although used mainly for evaluating the cervix, it also has a place in the investigation of vaginal and vulvar disease. It was first used by Hinselmann in 1925 in Germany but was not at all widely practised in the English-speaking world before 1970.

The instrument is shown in Figure 7.36; this is one of several types available which all have in common a movable base, adjustable supporting arm, bright light source and variable magnification. The focal length of the objective lens is between 200 mm and 400 mm, so that the head of the colposcope is some way from the patient's perineum during the examination, allowing room for manipulation of forceps, etc. The colposcopic examination is usually carried out as an outpatient procedure, with the patient in lithotomy position (or a more comfortable variant of that position). The cervix is exposed using a

sometimes the biopsies consist entirely of necrotic material and it is important that the assessment is made on the least necrotic areas.

The presence of all these features makes it reasonably easy for a pathologist to recognize the changes of irradiation. It is a different matter, however, to say whether the tumour is still viable or not and predict the outcome of the treatment; opinions are divided on whether this can, in fact, be done. It is not clear that the degenerative changes described above mean that the tumour is non-viable, as there is an overlap between some of these features and those of malignancy. However, if a biopsy does not show these features after treatment and is morphologically similar to the biopsy before treatment, with plentiful mitotic figures, then the tumour is probably resistant to treatment by irradiation.

Carcinoma of the cervix in pregnancy

The peak age of incidence of carcinoma of the cervix is slightly too old for invasive disease to be encountered frequently in pregnancy, and figures ranging from 1 per 2205 pregnancies (Hacker et al, 1982) to 1 per 6000 pregnancies (Ferenczy, 1982) have been quoted. In contrast, CIN 3 has an incidence of 1 case per 770 pregnancies.

Colposcopy has greatly helped the management of women with CIN in pregnancy; if invasive cancer can be excluded, then the patient can be left until after delivery before treatment is carried out. However, if colposcopy suggests that an invasive lesion is present, then confirmation that invasion is occurring must be obtained by biopsy. Because of the risk of haemorrhage and because a colposcopic biopsy is unlikely to be able to distinguish between microinvasive carcinoma and stage Ib occult invasive carcinoma, a wedge biopsy under general anaesthesia is advisable. If this wedge biopsy confirms invasion, but this is within the limits of microinvasion, then cone

biopsy is indicated, to exclude more advanced invasion elsewhere in the cervix (the FIGO definition of microinvasive carcinoma precludes its diagnosis on a small wedge biopsy). This is the only indication for cone biopsy in pregnancy, an operation which is hazardous because of the risk of abortion, premature labour or haemorrhage; colposcopy has taken the place of diagnostic conization for CIN. If the cone biopsy confirms the diagnosis of microinvasion with complete excision, then no further treatment is required, and the pregnancy is allowed to proceed to term. It is debatable whether further treatment is required after delivery.

If, on the other hand, the wedge biopsy or cone biopsy shows a stage Ib carcinoma, or if the cancer is clinically apparent at presentation and colposcopy is not needed, treatment for the tumour should be carried out without undue delay. If the pregnancy is in the first or second trimester, the fetus is sacrificed and radical treatment, either by surgery or radiotherapy, is carried out. After about 26–28 weeks, the interests of the unborn child have to be taken into account as well as those of the mother. In these circumstances, unless the disease is advanced, it may be reasonable to delay treatment for up to six weeks in order to increase the chances of life for the baby. In the accumulated series of Hacker et al (1982) the five-year survival rates obtained by obstetricians electing for immediate treatment were not significantly different from those obtained by obstetricians advocating a delay in treatment for up to two months. The same authors also found that the overall prognosis for all stages of cervical cancer in pregnancy, as well as for stage I disease, was similar to that in non-pregnant women. However, for more advanced disease, pregnancy appears to have an unfavourable effect on prognosis. They found an overall more favourable prognosis in pregnant patients but attributed this to a greater proportion of pregnant patients having stage I disease.

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4. 材料の取扱い、および検索方法

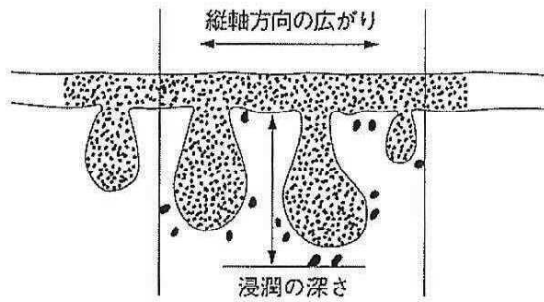
- (4) 脈管侵襲の有無・程度
- (5) 腔壁断端部での腫瘍の有無
- (6) 子宮傍組織浸潤の有無
- (7) 郭清リンパ節の転移の有無・部位別の個数
- (8) 病変以外の子宮の状態、および同時に切除された他臓器の状態

● pT 分類 (UICC TNM 分類第 7 版)

a) 子宮頸癌

- pTX 原発腫瘍の評価が不可能
- pT0 原発腫瘍を認めない
- pTis 上皮内癌
- pT1 子宮に限局
 - pT1a 顕微鏡によってのみ診断
 - pT1a1 深達度 ≤ 3.0 mm
水平方向進展 ≤ 7.0 mm
 - pT1a2 3.0 mm $<$ 深達度 ≤ 5.0 mm
水平方向進展 ≤ 7.0 mm
 - pT1b 臨床的に肉眼で認める、または顕微鏡的病巣が pT1a2 より大
 - pT1b1 ≤ 4.0 cm
 - pT1b2 > 4.0 cm
- pT2 子宮をこえるが、骨盤壁または腔の下 1/3 には達しない
 - pT2a 子宮傍組織に達しない
 - pT2a1 ≤ 4.0 cm
 - pT2a2 > 4.0 cm
 - pT2b 子宮傍組織に達する
- pT3 腔の下 1/3、および/または骨盤壁に達する、および/または水腎症、無機能腎を呈す
 - pT3a 腔の下 1/3 に達する
 - pT3b 骨盤壁に達する、および/または水腎症、無機能腎を呈す
- pT4 膀胱粘膜および/または直腸粘膜浸潤、小骨盤をこえる

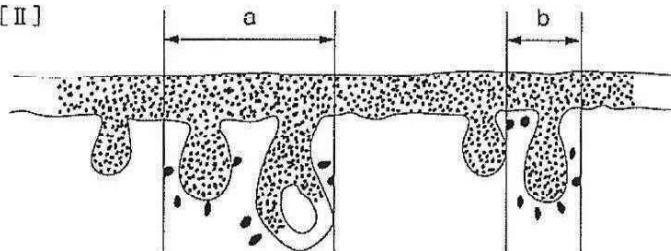
[I]



浸潤の深さと縦軸方向の広がりはいずれも組織標本上での計測により mm 単位で記載する。浸潤の深さと縦軸方向の広がりとは [I] のように直交関係にある。

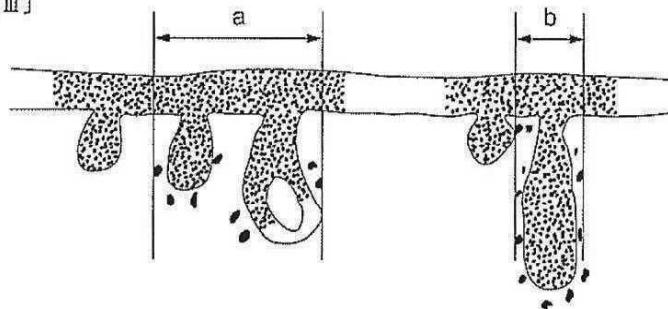
浸潤の深さは最深部の数値による。縦軸方向の広がりとは浸潤巣の最大の幅を計測する。なお、[II] [III] のように癌巣が skip lesion を形成している場合など、測定の対象部位が2カ所以上に及ぶ際には、それらのうちの最大値をもって当該症例の値とする。

[II]



[II] では、a 領域を縦軸方向の広がりおよび浸潤の深さを評価するための値とする。

[III]



[III] では、a 領域を縦軸方向の広がりをおよび浸潤の深さを評価する値とし、b 領域を浸潤の深さを評価するための値とする。

図 11 微小浸潤扁平上皮癌の計測

5) 扁平上皮癌 squamous cell carcinoma

重層扁平上皮への分化を示す浸潤癌のうち、微小浸潤扁平上皮癌をこえるものである。

扁平上皮癌は角化傾向を指標にして角化型、非角化型の2型に分類される。この2型で扁平上皮癌のほとんどを占め、いわゆる通常型に相当する。その他の特殊型は、WHO分類(2003年版)に基づいて併記する。これらの特殊型に分類される症例は他の成分を含まないもののみとする。扁平上皮癌では細胞質内に粘液染色陽性所見を呈する癌細胞を散見することがあるが、そうした場合でもいわゆる粘表皮癌 mucoepidermoid carcinoma といった名称は用いない。

4) 微小浸潤扁平上皮癌 **microinvasive squamous cell carcinoma**

微小浸潤を示す扁平上皮癌である。微小浸潤とは癌細胞の間質内浸潤を組織学的に確認することができ、かつ浸潤の深さが表層基底膜より計測して5 mm をこえず、またその縦軸方向の広がり7 mm をこえないものをいう。

本病変は Ia 期に分類される。なお、さらに浸潤の深さが 3 mm をこえないものを Ia1 期、それ以外のものを Ia2 期とする。

WHO 分類 (第 2 版, 1994 年) では、微小浸潤は特に定義されていない。前規約作成時には国際的にみて標準的な基準がないために、微小浸潤の定義はわが国で独自に定めた (1978 年)。しかし、その後、国際産婦人科連合 (FIGO, 1994 年) の臨床病期分類に具体的な定義が示された。したがって、本規約の微小浸潤扁平上皮癌の定義は基本的には FIGO の基準にあわせた。国際的にも通用する基準設定を意図したためである。このために、微小浸潤の定義は前規約と本規約とでは違いが生じた (表 2)。なお、FIGO の基準とは違い、本規約では浸潤の深さの測定基点を表層基底膜のみに限っている。つまり、腺上皮の基底膜を計測の基点とはしない。このように定めても進行期の判定に支障をきたす症例はほとんどなく、また基点を 1 つにしたほうが煩雑さを回避できると考えられるからである。

わが国の前規約における微小浸潤癌 **microinvasive carcinoma** は、本規約によれば Ia1 期にほぼ相当する。浸潤の深さ 5 mm のものまでが微小浸潤扁平上皮癌に含まれるため、Ia 期症例全体としては、前規約の基準にもとづく場合よりも広い範囲を包括している。

なお、本規約では癒合浸潤 **confluent invasion**、脈管侵襲 **vessel permeation** は、所見として記載するにとどめ、微小浸潤扁平上皮癌の診断は計測値のみによってなされる。これも前規約とは異なる点である。

表 2. 扁平上皮癌の微小浸潤—組織所見と臨床進行期の関係—

	浸潤の深さ*1		縦軸方向の広がり*2		癒合浸潤 あり*3	脈管侵襲 あり*3
	3 mm 以内	3 mm~5 mm 以内	7 mm 以内	7 mm をこえる		
本規約	Ia1 期	Ia2 期	Ia1 期 Ia2 期	Ib 期	Ia1 期 Ia2 期	Ia1 期 Ia2 期
前規約	Ia 期	Ib 期	Ia 期 Ib 期	Ia 期 Ib 期	Ib 期	Ib 期

* 1 縦軸方向の広がり 7 mm 以内に限定。

* 2 浸潤の深さ 5 mm 以内に限定。

* 3 浸潤の深さ 5 mm 以内かつ縦軸方向の広がり 7 mm 以内に限定。

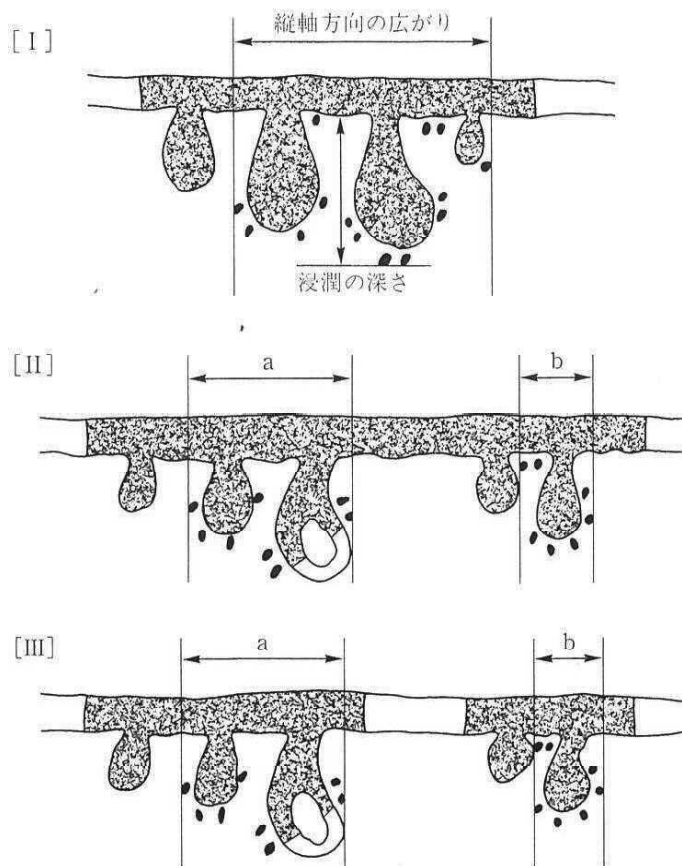


図 8. 微小浸潤扁平上皮癌の計測

浸潤の深さと縦軸方向の広がりはいずれも組織標本上での計測により mm 単位で記載する。浸潤の深さと縦軸方向の広がりとは [I] のように直交関係にある。

浸潤の深さは最深部の数値による。縦軸方向の広がりとは浸潤巣の最大の幅を計測する。なお、[II] [III] のように癌巣が skip lesion を形成している場合など、測定の対象部位が 2 ヶ所以上におよぶ際には、それらのうちの最大値をもって当該症例の値とする。図では $a > b$ なので、 a を縦軸方向の広がりとして評価するための値とする。

[注 1] 浸潤範囲の評価には、浸潤の深さと縦軸方向の広がりを組織標本上で計測する。浸潤の深さの計測の基点は浸潤巣の直上域の最も浅い表層基底膜とする。縦軸方向とは子宮頸部と底部を結ぶ方向を意味するもので、組織標本による鏡検の際には通常は水平方向として認識される (図 8)。この計測は微小浸潤の評価のためのもので、病変全体の広がりを意味するものではない。

[注 2] 癒合浸潤、脈管侵襲の存在する場合は必ず所見として記載する。

[注 3] 浸潤性増殖が疑われても、その確認が得られない場合には上皮内癌とし、0 期に入れる。

[注 4] 上記の診断は円錐切除またはそれに準じた方法による。

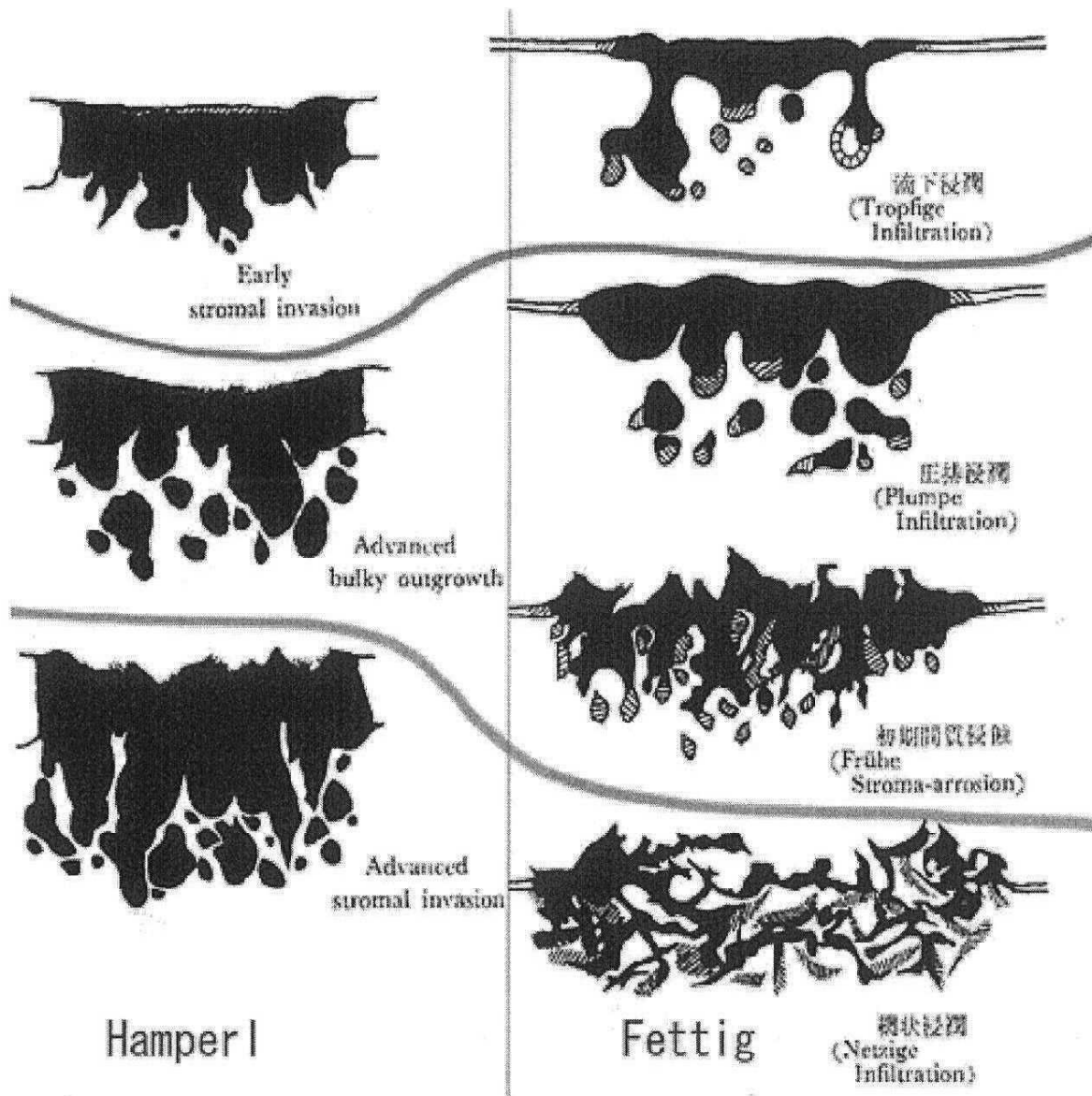


子宮頸癌、扁平上皮癌、CCla 診断基準の変遷

1. 1977年（昭和52年）、子宮頸癌Ia期分類基準試案

「浸潤の深さが直上の扁平上皮層基底膜より3mm以内。

（ただし、下図赤線の癒合浸潤 confluent invasion と脈管侵襲 vascular permeation はIb期とする）」



2. 1987年（昭和62年）、子宮頸癌取扱い規約、第1版（野田起一郎）

Squamous:

dysplasia: mild, moderate, severe,
CIS,

microinvasive: Ia 同上

frankly invasive SqCC

Adeno:

glandular dysplasia

AIS

microinvasive: Ia: 辺縁平滑な芽出 budding (+)

frankly invasive Adenoca.

3. 1997年(平成9年)、子宮頸癌取扱い規約、第2版(工藤隆一)

Squamous:

papilloma, condyloma acuminatum,

dysplasia: mild (CIN1), moderate (CIN2), severe (CIN3), CIS (CIN3),

microinvasive SqCC:

Ia1 浸潤: 深さ3mm以内、長さ7mm以内、

Ia2 浸潤: 深さ5mm以内、長さ7mm以内、

脈管侵襲 vascular permeation は病期に反映しない。

frankly invasive SqCC,

Adeno:

endocervical polyp, mullerian papilloma,

glandular dysplasia,

AIS,

microinvasive Adnoca: Ia, 辺縁平滑な芽出 budding (+)

frankly invasive Adenoca.

4. 2012年(平成24年)、子宮頸癌取扱い規約、第3版(嘉村敏治)

Squamous:

papilloma, condyloma acuminatum,

CIN: CIN1 (mild dysplasia, low SIL), CIN2 (moderate dysplasia, high SIL),

CIN3 (high SIL),

microinvasive SqCC:

Ia1 浸潤: 深さ3mm以内、長さ7mm以内、

Ia2 浸潤: 深さ5mm以内、長さ7mm以内、

脈管侵襲 vascular permeation は病期に反映しない。
frankly invasive SqCC,

Adeno:

glandular dysplasia,

AIS,

microinvasive Adnoca:

Ia1 浸潤：深さ 3mm 以内、長さ 7mm 以内、

Ia2 浸潤：深さ 5mm 以内、長さ 7mm 以内、

脈管侵襲 vascular permeation は病期に反映しない。

frankly invasive Adenoca.



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