

Original Article

Defining the Cervical Transformation Zone and Squamocolumnar Junction: Can We Reach a Common Colposcopic and Histologic Definition?

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Summary: Quality assurance and research in colposcopy and cervical pathology require standardized terminologies and reporting. However, clinical and histologic definitions of the cervical transformation zone (TZ) and squamocolumnar junction (SCJ) vary considerably. We aimed to identify areas of agreement and areas where work is required to standardize the definitions of the TZ and the SCJ. We conducted a survey among the board members of the European Federation of Colposcopy member societies and members of the International Society of Gynecological Pathologists. Overall, 22 expert colposcopists and 34 gynecologic pathologists responded. There was broad agreement that the TZ is the area where squamous metaplasia has occurred. There was consensus that the original SCJ can appear colposcopically indistinct in cases of maturation of the metaplastic squamous epithelium but can be identified histologically by the presence of the so-called last cervical gland. It was agreed that the border between the metaplastic squamous epithelium and the columnar epithelium on the surface of the cervix is called the new SCJ. Areas where work is required include the questions as to whether the cervical crypts lined by columnar epithelium in the field of squamous metaplasia are an integral part of the TZ or not and whether the individual microscopic borders between the metaplastic squamous epithelium of glandular crypts and the residual columnar epithelium of glandular crypts should be considered as part of the new SCJ or not. This paper is a step in an attempt to standardize colposcopic and histologic definitions among colposcopists and pathologists. **Key Words:** Cervix—Transformation zone—Squamocolumnar junction—Quality assurance—Terminology.

The concept of transformation from a glandular epithelium to a squamous epithelium (squamous metaplasia) is central to the understanding of the pathogenesis of cervical squamous cell carcinomas.

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The distribution of squamous cervical cancer precursors correlates with the extent of the transformed metaplastic squamous epithelium, typically referred to as the transformation zone (TZ) (1,2). The original squamocolumnar junction (SCJ) represents the border between the original squamous epithelium and the metaplastic squamous epithelium of the TZ. The border between the transformed metaplastic squamous epithelium of the TZ and the mucinous columnar epithelium of the cervix is the new SCJ (1,2). Within the TZ, the World Health Organization (3) recognizes two types of high-grade squamous intraepithelial lesion (HSIL): classic HSIL and thin HSIL (3). Classic HSIL develops through a low-grade squamous intraepithelial lesion in mature stratified metaplastic squamous

epithelium of the TZ and in the original squamous epithelium of the cervix (3,4). Thin HSIL can develop in early metaplastic squamous epithelium of the TZ near the new SCJ without antecedent low-grade squamous intraepithelial lesion (5,6). Clinical documentation of whether the SCJ between the metaplastic squamous epithelium and the columnar epithelium can be visualized is important and is a quality indicator for colposcopy (7,8). The location of a lesion in relation to the TZ was reintroduced in the 2011 International Federation for Cervical Pathology and Colposcopy (IFCPC) colposcopic terminology (7,9).

Quality assurance and research in colposcopy and cervical pathology require standard terminologies and reporting. However, clinical and histologic definitions of the TZ and the SCJ vary considerably (1–3,7,10,11). At present, the most commonly used colposcopic definition of the TZ refers to the area where transformation has occurred, in other words the area of metaplastic epithelium between the original SCJ and the new SCJ (1,2,7). It refers to the columnar epithelium that has undergone metaplastic transformation into immature and mature squamous epithelium. Some colposcopists, however, refer to the TZ as the area where squamous metaplasia potentially may occur (10), rather than the area where squamous metaplasia has already occurred. Following this definition, the TZ would extend from the original SCJ all the way across the cervix and along the endocervix to the epithelium of the uterine isthmus. In histopathology practice, the term TZ usually refers to the area where squamous metaplasia has occurred. It may involve the surface epithelium and/or the crypts and can consist of immature and/or mature stratified metaplastic squamous epithelium. Metaplasia may be a focal process, and metaplastic squamous epithelium may be bordered by mucin-producing columnar epithelium, both on the surface and in the glands (Figs. 1, 2). Given these variations, we undertook a survey of board members of the European Federation for Colposcopy (EFC) member societies and members of the International Society of Gynecological Pathologists (ISGyP). The aim was to identify areas of agreement and areas where work is required to standardize definitions of the cervical TZ and the SCJ.

METHODS

This internet-based survey was conducted among board members of EFC member societies and members of the ISGyP. The EFC comprises 30 member states and 5 associate member countries; the

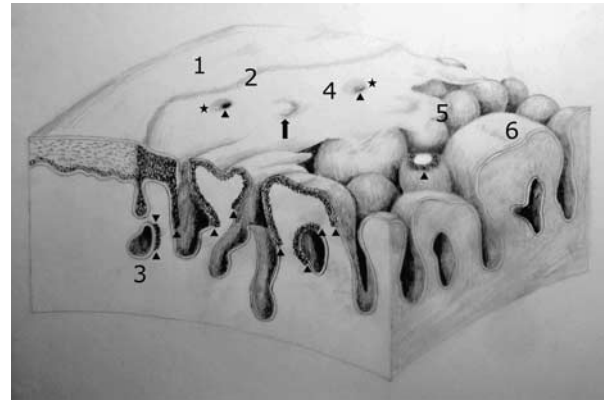


FIG. 1. Schematic illustration of the human cervix with types of epithelium, transformation zone, original, and new squamocolumnar junction (SCJ). The original squamous epithelium (1) is a glycogenated epithelium with a smooth surface without any glands in the underlying stroma. The original SCJ (2) represents the border between the original squamous epithelium (1) and the metaplastic squamous epithelium (4). By colposcopy of the cervical surface, the original SCJ is recognized as a thin line (2). In the third dimension, for example on histologic section, the so-called last cervical gland becomes visible (3). It is a lifelong anatomic landmark of the original SCJ. The transformation zone (TZ) (4) is the area between the original SCJ (2) and the new SCJ (5). The transformed metaplastic squamous epithelium is bordered by columnar epithelium (6), both on the surface and within glands. In colposcopy, the TZ (4) may show openings of cervical glands (*) and ovuli Nabothi (↑). In the third dimension, for example, on histologic sections, crypts become visible, which are lined by metaplastic squamous epithelium bordering columnar mucinous epithelium. The border between the transformed metaplastic squamous epithelium and the mucinous columnar epithelium is the new SCJ (5). It not only forms a sharp border at the cervical surface but also within the glands in the third dimension. It is controversial whether these multifocal borders (▲) of each individual gland are part of the new SCJ or not and whether the cervical crypts covered by columnar epithelium in the field of squamous metaplasia are an integral part of the TZ or not.

ISGyP is an international community of gynecologic pathologists. Board members of the national EFC member societies were circulated a consensus definition of the TZ and the SCJ, and were asked about the strength of agreement or disagreement (Table 1). ISGyP members were circulated different histologic definitions of the TZ (Table 2) and the SCJ (Tables 3, 4) available in the literature and were asked to identify the definition they considered best.

RESULTS

Overall, 22/35 (63%) member states and associated member countries of EFC responded. Of them, 16/22 (73%) reported complete agreement with the proposed colposcopic definitions of the TZ and the SCJ, and 6/22 (27%) suggested changes (Table 1). A total of 34 ISGyP members undertook the survey. Most ISGyP

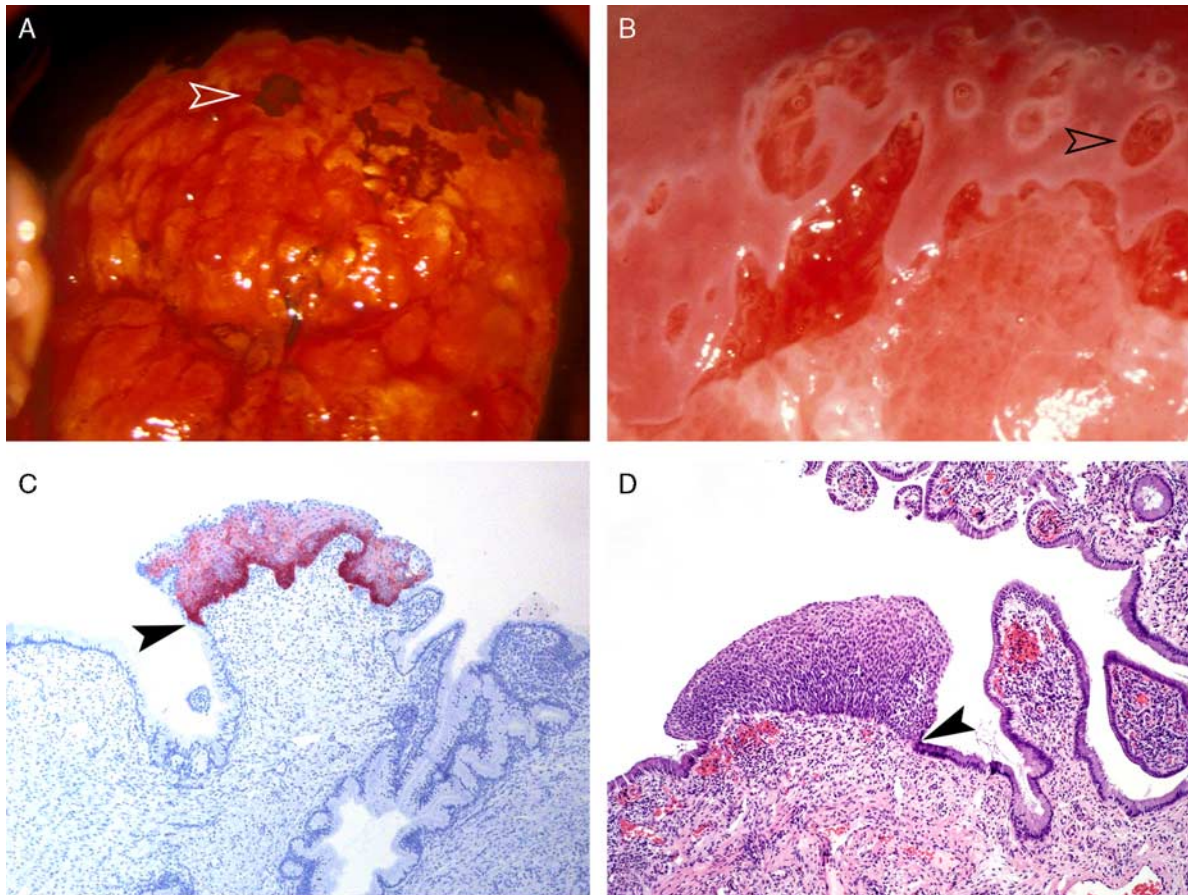


FIG. 2. Transformation (metaplasia) as a focal process near the squamocolumnar junction (SCJ). (A) After application of iodine (so-called Schiller test), the mature squamous epithelium turns dark brown. There are small islands with lighter shades of brown corresponding to areas of immature metaplastic squamous epithelium (\blacktriangleright) (from Girardi et al. (2)). (B) Transformation zone after application of acetic acid with a discontinuous area of mature squamous metaplasia (\blacktriangleright) surrounding patches of columnar epithelium. Each patch features its own individual SCJ, which can be recognized colposcopically. (C) Immunohistochemical stain with antibody to cytokeratin 17 showing a microscopically small field of immature squamous metaplasia (\blacktriangleright) (from Girardi et al. (2)). (D) Hematoxylin and eosin stain of a microscopically small field of high-grade squamous intraepithelial lesion within the columnar epithelium. SCJ of these individual fields (\blacktriangleright) can be seen only histologically.

members agreed that the TZ is the area where squamous metaplasia has occurred. Of them, 3/34 (9%) ISGyP members defined the TZ as an area in which transformation will potentially occur (Table 2). The answers (Table 2) yielded little agreement on the questions of whether the cervical crypts lined by columnar epithelium in the field of squamous metaplasia are an integral part of the TZ or not. In detail, 11/34 (32%) ISGyP members agreed that the cervical crypts lined by columnar epithelium in the field of squamous metaplasia are an integral part of the TZ; 10/34 (29%) did not agree and 8/34 (25%) were undecided. A total of 29/34 (85%) ISGyP members agreed that the original SCJ is the border between the original squamous epithelium and the original columnar epithelium (Table 3), and 32/34 (94%) ISGyP

members agreed that the new SCJ is the border between the metaplastic squamous epithelium and the mucin-producing columnar epithelium (Table 4). Following critical discussion, the authors of this paper suggest using the following colposcopic and histologic definitions of the TZ and the original and new SCJ, which take into account the survey results. These definitions are schematically illustrated in Figure 1.

Colposcopic Definitions

TZ

TZ is an area that extends from the smooth original squamous epithelium to the dark red columnar epithelium of the cervix. On examination,

TABLE 1. Colposcopic definitions of the TZ and the SCJ submitted to board members of EFC member societies

Definition	n (%)	
	Agreed	Changes required
The TZ is an area extending from the smooth original squamous epithelium to the dark red columnar epithelium of the cervix. The TZ often shows openings of cervical glands, ovuli Nabothi, small islands of residual columnar epithelium, and fine vascular pattern. It can appear as a nonspecific red area, but application of acetic acid turns the red epithelium grayish-white	16 (73)	6 (27)
The original SCJ is the border between the smooth original squamous epithelium and the squamous epithelium of the TZ after application of acetic acid. Colposcopically it can appear indistinct	19 (86)	3 (14)
The new SCJ is usually a sharp and step-like colposcopic border between the TZ and the glandular epithelium after application of acetic acid	20 (91)	2 (9)

EFC indicates European Federation for Colposcopy; SCJ, squamocolumnar junction; TZ, transformation zone.

it can appear as a nonspecific red area, but application of acetic acid turns the red epithelium to grayish-white depending on the degree of maturity of the metaplastic epithelium. The TZ often shows

TABLE 2. Histologic definitions of the TZ submitted to members of the ISGyP

Definition	Agreed [n (%)]
The TZ is where squamous metaplasia occurs. It extends from the original nonkeratinizing squamous epithelium of the ectocervix to the mucin-producing columnar epithelium of the endocervix. The columnar epithelium underneath the metaplastic epithelium is part of the TZ	11 (32)
The TZ is where squamous metaplasia occurs. It extends from the original nonkeratinizing squamous epithelium to the mucin-producing columnar epithelium of the cervix. The columnar epithelium underneath the metaplastic epithelium is <i>not</i> part of the TZ	10 (29)
The TZ is the zone in which transformation <i>will potentially</i> occur. It is characterized by the presence of metaplastic squamous epithelium, which may extend not only across the ectocervix but also to within the cervical canal (10)	3 (9)
The TZ is the zone between the original and current SCJ and the area around that junction where the epithelium is thinnest (3)	1 (3)
The TZ consists of surface squamous epithelium in continuity with surface columnar epithelium (SCJ) (11)	1 (3)

ISGyP indicates International Society of Gynecological Pathologists; SCJ, squamocolumnar junction; TZ, transformation zone.

TABLE 3. Histologic definitions of the original SCJ submitted to members of the ISGyP

Definition	n (%)	
	Agreed	Changes required
Original SCJ is the border between the original squamous epithelium and the original columnar epithelium (2)	29 (85)	5 (15)

ISGyP indicates International Society of Gynecological Pathologists; SCJ, squamocolumnar junction.

openings of cervical glands, ovuli Nabothi, small islands of residual columnar epithelium, and a fine vascular pattern.

Original SCJ

The original SCJ is the border between the smooth original squamous epithelium and the squamous epithelium of the TZ. Colposcopically it can appear indistinct.

New SCJ

The new SCJ is typically a sharp and step-like colposcopic border between the TZ and the columnar epithelium after application of acetic acid.

Histologic Definitions

TZ

Histologically the term TZ refers to the area where squamous metaplasia has occurred. It may involve the surface epithelium and/or the crypts and may consist of immature and/or mature stratified metaplastic squamous epithelium. Metaplasia may be a focal process and metaplastic squamous epithelium may be bordered by mucin-producing columnar epithelium, both on the surface and in glands.

TABLE 4. Histologic definitions of the new SCJ submitted to members of the ISGyP

Definition	n (%)	
	Agreed	Changes required
New SCJ is the border between the metaplastic squamous epithelium and the mucin-producing columnar epithelium (2)	32 (94)	2 (6)

ISGyP indicates International Society of Gynecological Pathologists; SCJ, squamocolumnar junction.

Original SCJ

The border between the original squamous epithelium and the original columnar epithelium.

New SCJ

The border between the metaplastic squamous epithelium and the mucin-producing columnar epithelium.

DISCUSSION

We present suggestions for colposcopic and histologic definitions with respect to the terms TZ and SCJ. This survey identified areas of agreement and areas where work is required to achieve scientifically sound and clinically workable definitions.

There was broad agreement between the expert colposcopists that the original SCJ can appear colposcopically indistinct in cases of maturation of the metaplastic squamous epithelium but can be identified histologically by the presence of the so-called last cervical gland. It was agreed that the border between the metaplastic squamous epithelium and the columnar epithelium on the surface of the cervix is called the new SCJ (Table 1). The responses showed a broad agreement between gynecologic pathologists that the TZ is the area where squamous metaplasia has occurred (Table 2). Biopsies obtained from the TZ may show the following structures: mature and immature squamous surface epithelium, crypts lined by columnar and by mature and immature metaplastic squamous epithelium, and the intervening vascularized stroma (Fig. 1).

The suggestions for colposcopic and histologic definitions of the TZ and the SCJ (see the Results section) are based on the principle that in human prenatal life, a dual mechanism for cervical epithelialization is seen: the epithelium of the vaginal fornices and the original squamous epithelium of the cervix up to the original SCJ is of vaginal Mullerian origin, whereas the columnar epithelium of the cervix is of uterine Mullerian origin (12,13). The original SCJ can be recognized within the cervical canal from week 24 onwards. In late fetal life, columnar epithelium invaginates from the surface of the cervix into the underlying stroma to develop cervical glands. These glands migrate in a caudal and oblique direction. Consequently, the original SCJ descends toward the ectocervix to produce an ectopy in newborns (12,13). The original SCJ is a lifelong anatomic landmark defined by the so-called last

cervical gland, a concept introduced by Hamperl et al. (14). The term transformation refers to metaplastic transformation of columnar epithelium to squamous epithelium (squamous metaplasia), which occurs after menarche due to vaginal pH changes, hormonal changes, mechanical irritation, and chronic inflammation (1,2). The SCJ is thus shifted by the development of the TZ to some distance from the original SCJ, resulting in a new SCJ (15). In consequence, the original SCJ represents the anatomic landmark between the original squamous epithelium and the metaplastic squamous epithelium of the TZ, whereas the new SCJ separates the metaplastic squamous epithelium of the TZ and the columnar epithelium.

The survey also demonstrated the difficulties in reconciliation between colposcopic and histologic definitions (Fig. 1): colposcopically, only the surface of the cervix can be seen; in other words, only 2 dimensions can be visualized. In biopsies, however, another (third) dimension becomes visible, namely, the tissue underneath the surface epithelium of the cervix consisting of stroma and glandular crypts. Colposcopy and histology can show multifocal patches of remnant columnar epithelium between areas of squamous metaplasia both on the surface and also within the glandular crypts. Each of these patches features its own microscopic SCJ (Figs. 1, 2). The existence of these multiple microscopic junctions throughout the TZ has not been addressed in the recent literature on the SCJ (16–22).

Areas where further work is required include the questions of whether the cervical crypts lined by columnar epithelium in the field of squamous metaplasia are an integral part of the TZ or not and whether the individual microscopic borders between the metaplastic squamous epithelium of glandular crypts and the residual columnar epithelium of glandular crypts should be considered as part of the new SCJ or not.

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REFERENCES

1. Kurman RJ. *Blaustein's Pathology of the Female Genital Tract*. New York: Springer; 2012.
2. Girardi F, Reich O, Tamussino K. *Burghardt's Colposcopy and Cervical Pathology*. New York: Thieme; 2015.
3. Stoler M, Bergeron C, Colgan TJ, et al. Tumours of the cervix: squamous cell tumours and precursor lesions. In: Kurman JR,

- Carcangin ML, Herrington CS, et al, eds. *World Health Organization Classification of Tumours of the Female Reproductive Organs*. 4th ed. Lyon: IARC press; 2014:172–82.
4. Woodman CB, Collins SI, Young LS. The natural history of cervical HPV infection: unresolved issues. *Nat Rev Cancer* 2007;7:11–22.
 5. Reich O, Regauer S. Two major pathways for development of high-grade squamous intraepithelial lesions of the cervix. *Am J Surg Pathol* 2014;38:1579–80.
 6. Reich O, Regauer S. Thin HSIL of the cervix: detecting a variant of high-grade squamous intraepithelial lesions with a p16INK4a—antibody. *Int J Gyn Pathol* 2017;36:71–5.
 7. Bornstein J, Bentley J, Bösze P, et al. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. *Obstet Gynecol* 2012;120:166–72.
 8. Moss EL, Arbyn M, Dollery E, et al. European Federation of Colposcopy quality standards Delphi consultation. *Eur J Obstet Gynecol Reprod Biol* 2013;170:255–8.
 9. Hammes LS, Naud P, Passos EP, et al. Value of the International Federation for Cervical Pathology and Colposcopy (IFCPC) Terminology in predicting cervical disease. *J Low Genit Tract Dis* 2007;11:158–65.
 10. Singer A, Khan AM, Bornstein J. *Cervical and Lower Genital Tract Precancer*. Oxford: Wiley Blackwell; 2014.
 11. Mukonoweshuro P, Oriowolo A, Smith M. Audit of the histological definition of cervical transformation zone. *J Clin Pathol* 2005;58:671.
 12. Fritsch H, Hoermann R, Bitsche M, et al. Development of epithelial and mesenchymal regionalization of the human fetal utero-vaginal anlagen. *J Anat* 2013;222:462–72.
 13. Reich O, Fritsch H. The developmental origin of cervical and vaginal epithelium and their clinical consequences: a systematic review. *J Low Genit Tract Dis* 2014;18:358–60.
 14. Hamperl H, Kaufmann C, Ober KG, et al. Erosion of the portio: formation of pseudoerosion, ectropion and pavement cell epithelialization of the cervical glands on the surface of the portio. *Virchows Arch* 1958;331:51–71.
 15. Pixley E. Morphology of the fetal and pretubertal cervicovaginal epithelium. In: Jordan JA, Singer A, eds. *The Cervix*. Philadelphia: Saunders; 1976.
 16. Herfs M, Yamamoto Y, Laury A, et al. A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer. *Proc Natl Acad Sci USA* 2012; 109:10516–21.
 17. Herfs M, Vargas SO, Yamamoto Y, et al. A novel blueprint for ‘top down’ differentiation defines the cervical squamocolumnar junction during development, reproductive life, and neoplasia. *J Pathol* 2013;229:460–8.
 18. Herfs M, Parra-Herran C, Howitt BE, et al. Cervical squamocolumnar junction-specific markers define distinct, clinically relevant subsets of low-grade squamous intraepithelial lesions. *Am J Surg Pathol* 2013;37:1311–8.
 19. Mirkovic J, Howitt BE, Roncarati P, et al. Carcinogenic HPV infection in the cervical squamo-columnar junction. *J Pathol* 2015;236:265–71.
 20. Herfs M, Somja J, Howitt BE, et al. Unique recurrence patterns of cervical intraepithelial neoplasia after excision of the squamocolumnar junction. *Int J Cancer* 2015;136:1043–52.
 21. Herfs M, Crum CP. Cervical cancer: squamocolumnar junction ablation—tying up loose ends? *Nat Rev Clin Oncol* 2015;12:378–80.
 22. Franceschi S. Past and future of prophylactic ablation of the cervical squamocolumnar junction. *Ecancermedicalscience* 2015;29:527.