The evolution of the management of «CIN» lesions

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Summary: During the years 1961-1986 a total of 378 CIN lesions were diagnosed among 4875 women screened for cervical pathology; 285 of them were followed-up for a minimum of 5 years.

All 169 cases diagnosed as CIN-3 and 18 classified as CIN-2 were treated surgically, whereas 89 patients diagnosed as CIN-1 and 65 classified as CIN-2 were treated conservatively. Finally, 37 cases (23 diagnosed as CIN-1 and 14 diagnosed as CIN-2) did not receive any treatment.

Of the 187 women treated surgically, 6 (3.8%) showed, within the five year follow-up period, progression or recurrence of the disease, which necessitated either additional surgery or radiation; 5 of these cases had been classified as severe dysplasia (CIN-3).

Recurrence or progression necessitating major surgery, occurred in 8 (5.1%) of the 154 patients treated conservatively; 5 of these cases were classified as moderate dysplasia (CIN-2).

The data indicate that present diagnostic procedures allow a better selection of patients to be submitted to surgery, increasing the proportion of those treated conservatively, without jeopardizing their prognosis.

Key words: CIN-lesions; Cervical carcinoma management.

INTRODUCTION

Since Papanicolau first introduced his simple method of screening for cervical neoplasia, this group of lesions was generically lumped together as "premalignant lesions" often considered as benign [1-7]. It was not until 1956 that evidence became available indicating that, in fact, some of these cases would eventually progress to invasive carcinoma [8-10]. This realization forced pathologists to devise a better classification of non-invasive cervical lesions, which were divided into "dysplasia", considered as benign, and "carcinoma in situ" [11]. Because of the belief that in some cases the disease would progress, therapeutic management often depended on the physician's own convinction or on the pathologists's interpretation [12, 13].

A further evolution in the understanding of the natural history of pre-malignant cervical pathology, was the classification proposed by Richardt [14], who labelled all cervical lesions as "cervical intraepithelial neoplasia" (CIN), believing that they were all part of the same process and, therefore, all could possibly progress towards invasive carcinoma. As a consequence, all types of CIN required treatment; as a further inference though, a large number of women could be treated

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Clin. Exp. Obst. Gyn. - ISSN: 0390-6663
XX, n. 3, 1993

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conservatively, avoiding the mutilation inherent in radical surgery ([15–17]).

In the last two decades the knowledge and therefore the classification of cervical intraepithelial neoplasia continued to evolve thanks to two major factors: first, the widespread utilization of mass screening programmes, which has greatly increased the number of cases of pre-invasive cervical carcinoma detected ([18, 19]); second, an overall increased incidence of this type of lesions, with a concomitant lowering of the age at which pre-neoplastic lesions can be observed ([20-22]).

This last phenomenon has been attributed to several factors: a better early diagnosis ([5, 23, 24]); an early onset of sexual activity and a multiplicity of partners early in life ([25]); and even the use of oral contraceptives ([26, 27]).

MATERIALS AND METHODS

Clinical material

During the years 1961 - 1986, 4875 women were sent for further evaluation to the Cervical Pathology Unit of the First Institute of Obstetrics and Gynaecology of the University la Sapienza of Rome.

Among these outpatient women a total of 378 cases of cervical dysplasia were diagnosed.

All lesions were originally classified according to the system utilized at the time of observation; they were subsequently all-reanalyzed and reclassified using the CIN system.

The classification of all cases observed is reported in Table 1. Overall, 112 cases (29.6%) were diagnosed as mild dyspasia (CIN-1), 97 (25.7%) as moderate dysplasia (CIN-2) and 169 (44.7%) as severe dysplasia (CIN-3).

Table 1. — *Overall classification of the lesions observed during the 25 year period of analysis.*

Grade	No.	%
CIN-1	112	29.6
CIN-2	97	25.7
CIN-3	169	44.7
Totals	378	100.0

Every case was re-classified according to Richardt ([14]).

Treatment options

All patients were managed in one of the four following ways:

a) *Follow-up without treatment:* a number of women refused therapy and were followed without treatment. Some were subsequently lost when they failed to return to the clinic.

b) *Conservative treatment:* this consisted of diathermocoagulation, diathermy ablation or laser vaporization. The latter became the treatment of choice from 1980 onwards.

c) *Cervical conization:* the procedure identified as "cold knife" was utilized, according to its standard technique.

d) *Hysterectomy:* three modalities were employed: abdominal hysterectomy with vaginal cuff; radical abdominal hysterectomy according to Wertheim-Novak; radical vaginal hysterectomy according to Schauta-Amreich.

RESULTS

Age at diagnosis

The age distribution of women at the time of diagnosis is shown in Table 2.

Table 2. — *Age of patients at time of diagnosis.*

Age group	CIN-1	CIN-2	CIN-3
< 21	5	3	–
21-30	31	38	49
31-40	47	39	65
41-50	20	13	36
51-60	5	2	15
61-70	3	2	3
> 70	112	97	169
Total	112	97	169

Eight cases of CIN-1 and CIN-2 were detected in subjects below age 21, whereas 118 cases were identified in women between 21 and 30 years of age. This means that 33.3% of all cases with mild and moderate dysplasia were 30 years or less.

Among women with CIN-1 lesions, 49 (29.0%) were also between the age of 21 and 30.

Management

The distribution of patients among the various treatment options is indicated in Table 3.

Table 3. — *Overall management of CIN lesions over the 25 year period.*

	Number of cases		
	CIN-1	CIN-2	CIN-3
No treatment	23	14	–
Conservative therapy	89	65	–
Cervical conization	–	9	48
Hysterectomy	–	9	121
Totals	112	97	169

Overall, 37 (23 CIN-1 and 14 CIN-2) women did not receive any treatment: when diagnosed they refused immediate therapy; follow-up was attempted but, in no case, was this possible for more than 14 months.

Conservative management

This was selected for women of all ages; in total, it was utilized in 89 cases diagnosed as "mild" (CIN-1) and 65 diagnosed as "moderate" dysplasia (CIN-2), as illustrated in Table 4.

Table 4. — *Conservative management selected for mild (CIN-1) and moderate (CIN-2) dysplasia.*

	CIN-1		CIN-2	
	No.	%	No.	%
Diathermocoagulation	42	47.2	28	43.0
Laser vaporization	29	32.5	24	36.9
Diathermy ablation	18	20.3	13	20.1
Totals	89	100.0	65	100.0

Conservative therapy was based more on age considerations than on the degree of dysplasia. However, no case classified as CIN-3 was selected for conservative treatment.

Figure 1 illustrates how conservative management increased over the years, being maximal in the period 1981-86.
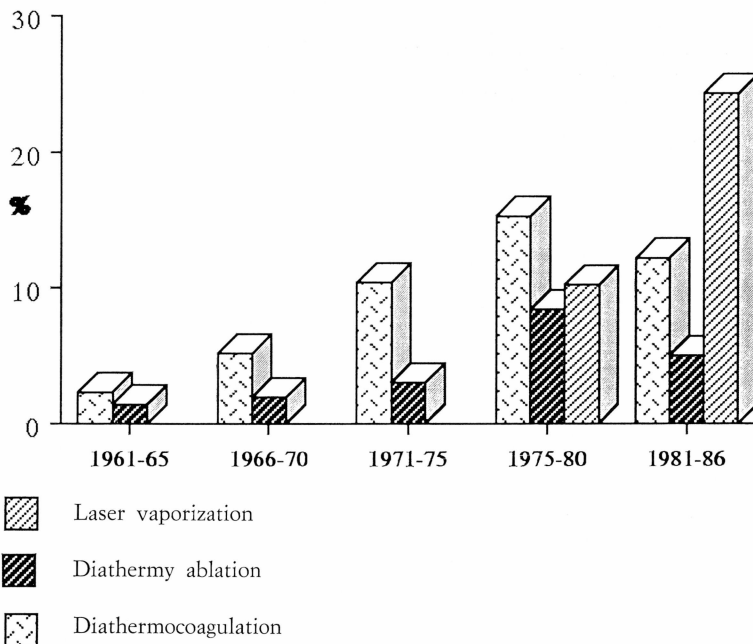

Fig. 1. — Number of patients with CIN-I and CIN-II managed conservatively during the 25 year period of observation.

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Surgery

This was selected in 187 cases; both conservative and demolitive techniques were utilized as indicated in Table 5.

Table 5. — *Surgical procedures selected for moderate (CIN-2) and severe (CIN-3) dysplasia.*

	No.	%
Cervical conization	57	30.5
Hysterectomy with vaginal cuff	42	22.4
Vaginal radical hysterectomy	85	45.5
Abdominal radical hysterectomy	3	1.6
Totals	187	100.0

Cervical conization: this technique was preferred in younger women. Conization was selected in 9 cases of CIN-2 (9.3%) and in 48 classified as CIN-3 (28.4%). Of the latter, 40 women were aged forty or below.

Hysterectomy: was the method of choice in 130 patients; 42 women were managed by total hysterectomy with vaginal cuff; 85 by vaginal radical hysterectomy and 3 by radical abdominal hysterectomy.

Overall, the vaginal route was the one utilized more frequently, chosen in 45% of all women.

Although hysterectomy was used in patients of all ages and grades, the majority of women treated in this way belonged to CIN-3; furthermore, they were older than the subjects treated conservatively, as illustrated in Table 6.

Table 6. — *Age of patients treated by surgery.*

Age group	CIN-1	CIN-2	CIN-3
< 21	–	–	–
21-30	–	–	20
31-40	–	2	54
41-50	–	6	31
51-60	–	1	14
61-70	–	–	2
> 70	–	–	–
Total		9	121

Complications following surgery

Radical vaginal hysterectomy: fatal complications occurred only once; in 1965 a patient died due to massive haemorrhage. The major non fatal complications were: serious haemorrage (7 cases), bladder lacerations (6 cases) and thromboembolism (2 cases). Conservative surgery complications were rare: copious bleeding during cone biopsy occurred in only 2 cases.

Follow-up

Satisfactory follow-up at 5 years was achieved in 285 of the 341 patients treated; the overall loss to follow-up at 5 years was therefore 16.4% (Table 7).

Table 7. — *Post-operative complications of surgically treated patients.*

Treatment	No.	Exitus	Hae-morrha-ge	Lace-ration	Throm-boem-bolism
Radical hysterectomy:					
vaginal	85	1	4	5	2
abdominal	3	–	–	–	–
Hysterectomy with vaginal cuff	42	–	1	1	
Cervical conization	57	–	2	–	–
Totals	187	1	7	6	2

Of the 89 women classified as CIN-1 and treated conservatively, 73 or 81.9% were followed for the minimum period of 5 years.

Of the 83 patients classified as CIN-2, 68 or 87.6% were properly followed, whereas satisfactory follow-up of the 169 women with CIN-3 lesions was achieved for 144 or 85.2%. Post-operative surveillance was slightly higher (43 out of 48, or 89.5%) in subjects treated with conization, than in those submitted to hysterectomy (101 out of 121, or 83.4%).

Recurrence or progression

Among women treated conservatively, recurrence was observed in 2 of the 73 CIN-1 (2.7%), whereas progression occurred in 1 of them. Figures for CIN-2 were 3 (5.2%) for recurrence and 2 (3.5%) for progression. One recurrence was observed among the 9 CIN-2 cases treated by conization and 1 (0.9%) among the 101 CIN-3 on whom simple hysterectomy was performed. The data are summarized in Table 8.

Table 8. — *Recurrence or progression in the 285 cases followed for a minimum of five years.*

Grade	Conservative management		Conization		Hysterectomy	
	Recurrence or Progression No.	%	Recurrence or Progression No.	%	Recurrence or Progression No.	%
CIN-1	3	4.10	–	–	–	–
CIN-2	5	8.77	1	16.6	–	–
CIN-3	–	–	4	9.3	1	0.9
Totals	8	5.1	5	8.7	1	0.9

DISCUSSION

Before Richardt ([2, 11]) came-up with the notion that all dysplastic lesions of the cervix are potentially malignant and represent an intra-epithelial neoplasia, treatment was conditioned by the confusion in terminology, the often differing views of pathologists and the personal experience of the clinician. This is why therapeutic strategies ranged from observational management to radical surgery. This in turn led to extensive surgical management which – in the mind of many – was justified by the low post-operative recurrence it produced ([28]).

Under the circumstances, it was not easy to advocate a conservative management for at least the first two grades of CIN ([15]). Indeed, during the period 1961-1976 those responsible for our Cervical Pathology Unit felt comfortable with advocating either radical vaginal hysterectomy or abdominal hysterectomy with vaginal cuff, taking into account the most common route of diffusion of cervical carcinoma ([28]), although a less demolitive approach was taken by most clinicians working in the field ([16]). The vaginal route seemed at the time a preferred technique because it allows a better visualization of the lesions ([17, 28]). In spite of this active – often excessive – approach, some have described a recurrence rate as high as 8.1%, following simple hysterectomy in the case of lesions classified today as CIN-3 ([29]). This, however, can be attributed to faulty diagnostic procedures, since, in as many as 25% of these cases, invasive carcinoma was subsequently found.

The advent of the new classification has allowed a re-evaluation of the need for radical surgery; for this reason starting from 1976, simple conization was introduced in our Unit as the treatment of choice in the case of CIN-3. Four years later the very comprehensive review of 1609 cases published by Burghardt and Holzen ([17]), provided the statistical evidence documenting the safety of this major change in the management of CIN-3 lesions.

When proper diagnosis has been established, the efficacy of minor surgical procedures has been properly documented: Burghardt and Holzen ([17]) had 0.3% of recurrence after full conization, followed by serial step-sectioning of the surgical specimen. If incomplete conization was performed, recurrence was observed in 8.5% and progression in 2.2% with one case out of nine following conization. In our series, recurrence after conservative management was 5.1% and 8.7% after conization. It must be stated, however, that proper, long-term follow-up of these patients is mandatory, since invasive carcinoma, following conservative management, can appear many years later ([30]). These data compare well with those ob-

tained after surgery: Burghardt reports recurrence occurring in 2.8% and progression in 0.7% following radical vaginal hysterectomy and abdominal hysterectomy with vaginal cuff and 3.4% of recurrence and 0.6% of progression following simple hysterectomy. Our figures are 0.9% (one case of recurrence) following simple hysterectomy with no cases after radical hysterectomy.

In conclusion, the evolution of the management of intra-epithelial cervical neoplasia towards a much more conservative approach is due first of all to better diagnostic procedures, which now include: targeted biopsies under the colposcope and microcolpohysteroscopy; also of importance is the new overall classification of these lesions. This evolution has allowed the preservation of fertility in a number of young women, a reduction of intra- and post-operative complications and a drastic reduction of radical, mutilating surgery, without any loss of therapeutic efficacy.

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