POST TREATMENT BEHAVIOUR OF CERVICAL INTRAEPITHELIAL NEOPLASIA - GRADE III

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SUMMARY

The behaviour in time of cervical intraepithelial neoplasia grade III has been evaluated in 141 patients treated for CIN III.

It was observed that surgery ensures the higher healing-rate, whether histerectomy or conization are performed, while diathermocoagulation seems unsatisfactory.

Colposcopy, colpocytology and sight biopsies of the cervical canal, portio and vagina, which provide a precise lesion-map, are then essential investigations to make the subsequent treatment a truly radical one.

A very close monitoring of patients, treated for CIN III, seems required in the first year after surgery, when we observed the highest rate of persistences and recurrences, while, subsequently, their incidence decreases as time passes by.

Personalized prognostic evaluation in cases of cervical intraepithelial neoplasia (CIN) has not yet been clearly stated, nor are the consequent therapeutic choices and follow-up schedules ([1, 3, 4, 6, 7, 8, 9, 10, 12]); the problem seems even harder when those lesions are considered that cannot be properly classed among CIN lesions, though they are commonly believed to be their precursors, namely reserve cell atypical hyperplasia and squamous atypical metaplasia.

The collection into the class of CIN ([2, 5, 11, 15]) of lesions with different previous denominations and hardly linked by any apparent connection, led to the achievement of a further landmark which contributed to improving the knowledge of CIN natural history, acquiring new significant data which are also confirmed by studies of electron microscopy, cytochemistry and cellular metabolism ([13]).

Indeed, as all CIN lesions of any degree share the same general characters and differ in quantitative but not in qualitative aspects, they are surely all steps of CIN natural history, which can thus be better understood in all the connections of its whole development.

In view of these new acquisitions we purposed to examine the evolution in time of CIN lesions grade III in relation to the therapies performed and the various cyto-histological aspects, to achieve more exact data on their invasion potentiality, and, possibly, to get speculatively interesting news.

MATERIAL AND METHODS

We studied 141 patients treated for cervical intraepithelial neoplasia grade III in our Clinic between 1970-1979.

The following parameters were evaluated:

— cyto-histological type: it was assessed as accurately as possible, by reviewing the cytologic and histologic specimens on which the diagnosis had been made. For this purpose we subdivided our cases according to the W.H.O. ([14]) classification, which best fits the aim of our study, as

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Table 1. — *CIN grade III response rate to all type therapy.*

Healing		Persistence		Recurrence		Persistence+Recurrence	
No.	%	No.	%	No.	%	No.	%
99	70.21	11	7.80	31	21.98	42	29.78
		CIN I 4	2.83	CIN I 19	13.47	CIN I 23	16.30
		CIN II 3	2.12	CIN II 2	1.41	CIN II 5	3.54
		CIN III 4	2.83	CIN III 10	7.09	CIN III 14	9.92

it includes all-degree lesions, from the precursors to the CIN itself, in its different morphological expressions.

The resulting definitions are as follows:

— atypical metaplasia: lack of differentiation and maturation of the cervical epithelium in which the basal or immature cells are dislocated in an abnormal position towards the surface, and show various degrees of atypia;

— severe dysplasia: some epithelial layers are substituted by cells in which the degree of atypia is very high. There is polarity loss and the cells, crowded, have voluminous and intensely coloured nuclei;

— carcinoma in situ: all, or nearly all, the epithelium shows carcinoma cellular characteristics without invasion of the stroma.

Whenever we found more than one lesion together, we classified the case according to the most serious one, that is the one with the highest oncogen risk and namely:

Atypical metaplasia < Severe dysplasia < Carcinoma in situ;

— performed treatment: conization, hysterectomy and diathermocoagulation;

— the results of post-treatment check-up investigations (colpocytology, colposcopy and eventually sight-biopsy), periodically performed up to the days of our study were grouped according to the following time-terms: 30 mo., 6 mo., 12 mo., 18 mo., 24 mo., 3 y.rs, 5 y.rs, 10 y.rs.

We defined as persistence the appearance of a CIN lesion grade I or II or III within 3-6 months from treatment, and as recurrence the appearance of the same lesion after 6 months from it.

RESULTS

Tables 1, 2, 3 and 4 describe the behaviour in time of the examined CIN grade III – cases, according to their cyto-histological type and to the performed treatment.

The evaluation of our whole series, independently from cyto-histological types and therapies (tab. 1), points out an healing rate of 70.21%, while the lesion

Table 2. — *CIN grade III response rate to the different types of therapy.*

Therapy			Healing		Persistence		Recurrence	
	No.	%	No.	%	No.	%	No.	%
Conization	72	51.06	50	69.44	8	11.11	14	19.44
					CIN I 4	5.55	CIN I 8	11.10
					CIN II 2	2.77	CIN II 1	1.38
					CIN III 2	2.77	CIN III 5	6.94
Histerectomy	61	43.26	50	81.96	1	1.63	10	16.39
					CIN I —	—	CIN I 7	11.47
					CIN II —	—	CIN II 1	1.63
					CIN III 1	1.63	CIN III 2	3.27
Diathermocoagulation	8	5.67	2	25	1	12.5	5	62.50
					CIN I —	—	CIN I 2	25
					CIN II 1	12.5	CIN II —	—
							CIN III 3	37.50
Total	141	100	102	72.34	10	7.09	29	20.56

Table 3. — *CIN grade III response rate to the surgical therapy (conization + isterectomy) and diathermocoagulation.*

Therapy			Healing		Persistence+Recurrence		
	No.	%	No.	%		No.	%
Surgical	133	94.32	100	75.18		33	24.82
					CIN I	19	14.39
					CIN II	4	3
					CIN III	10	7.52
Diathermocoagulation	8	5.67	2	25		6	75
					CIN I	2	25
					CIN II	I	12.5
					CIN III	3	37.5
Total	141	100	102	72.34		39	27.65

persisted in 7.80% of cases, 2.83% of which were CIN grade III; recurrences appeared in 21.98% of cases of which 7.09% were CIN grade III, 13.47% CIN grade I and 1.41% CIN grade II.

In short, 29.78% of cases presented a persistence or a recurrence, with a marked prevalence of the latter; in 9.92% of cases the type of recurrence or persistence was CIN III, which equally affected both groups.

We examined, then, the clinical results according to the different types of therapy. The lesion treatment in our series was co-

Table 4. — *CIN III response rate to all type therapy for each cyto-histological type.*

Cyto-histological type			Healing		Persistence		Recurrence	
	No.	%	No.	%	No.	%	No.	%
* Severe dysplasia	43	30.49	21	48.84	5	11.63	17	39.53
					CIN I 2	4.65	CIN I 10	23.25
					CIN II 3	6.97	CIN II 1	2.32
					CIN III —	—	CIN III 6	13.95
Carcinoma in situ	90	63.82	71	78.88	5	5.55	14	15.55
					CIN I 2	2.22	CIN I 9	9.99
					CIN II —	—	CIN II 2	1.11
					CIN III 3	3.33	CIN III 3	4.44
Atypical metaplasia	8	5.67	7	87.5	—	—	1	12.5
					CIN I —	—	CIN I 1	12.5
					CIN II —	—	CIN II —	—
					CIN III —	—	CIN III —	—
Total	141	100	99	70.21	10	7.09	32	22.69

* Note: *CIN III response rate to therapy excepted diathermocoagulation.*

Cyto-histological type			Healing		Persistence		Recurrence	
	No.	%	No.	%	No.	%	No.	%
Severe dysplasia	35	24.82	19	54.28	4	11.42	12	34.28
					CIN I 2	5.71	CIN I 8	22.85
					CIN II 2	5.71	CIN II 1	2.85
					CIN III —	—	CIN III 3	8.57

Fig. 1. — Percentual recurrence rate at the different considered time intervals.

nization in 72 cases, hysterectomy in 61 and diathermocoagulation in 8 cases.

By conization, a complete healing was achieved in 69.44% of cases, while persistence was present in 11.11% (2.77% CIN III) and recurrence occurred in 19.14% (9.94% CIN III).

By hysterectomy an higher healing-rate was obtained (81,96%), though persistences (1.63%-1.63% CIN III) and recurrences (16.39%-3.27% CIN III) were noted too.

By diathermocoagulation, performed in very few cases, the obtained result was absolutely unsatisfactory: healing in only 25%, persistence in 12.5% (no CIN III) and recurrence in 62.5% (CIN III in 37.5%). The difference between the surgical treatments can be considered very significant.

Then we have correlated CIN behaviour in time with the performed treatment and the cyto-histological type (tab. 4), better to interpret the above shown results and gain useful data for a proper settling of diagnostic and therapeutic schemes.

We observe that the highest healing-rate is found in atypical metaplasia (87.5%), followed by carcinoma *in situ* (78.88%) and by severe dysplasia (48.84%). So low an healing-rate in severe dysplasia is partly due to the type of treatment, as diathermocoagulation was performed in 8 cases, with a quite unsatisfactory efficacy.

This kind of therapy was never performed, on the contrary, in the other histoloigcal types of lesion.

The healing-rate of severe dysplasia, once diathermocoagulated lesions are excluded, is 54.28%, still much lower than in the other groups.

The highest number of persistences was found in cases of severe dysplasia, 11.63% (11.42% excluding diathermocoagulated lesions).

Persistence was noted in 5.55% of the cases of carcinoma *in situ*, CIN III type in 3.33%.

Table 5. — *Disease-free patient number at the different time intervals, calculated by transversal measurements of fictitious cohort behaviour.*

Time intervals	Time 0	Time 6 months	Time 12 months	Time 18 months	Time 24 months	Time 3 years	Time 5 years	Time 10 years
Disease free patient No.	100	60	36	26	21	17	15	13

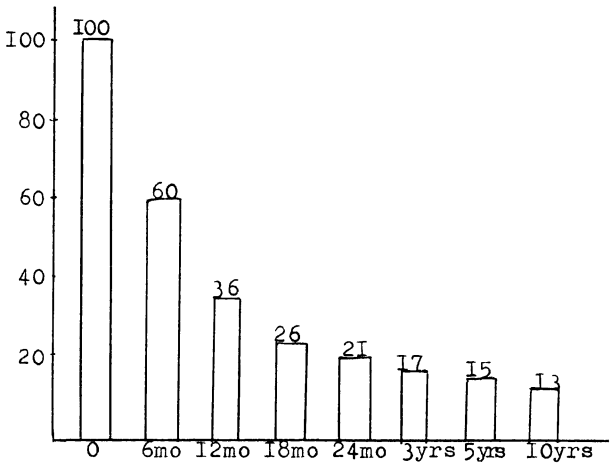

Fig. 2. — Graphic rapresentation of the data reported in table 6.

No persistence was noted in atypical metaplasia.

As to recurrences the trend is similar, with the highest number in severe dysplasia (39.53%-34.28% without diathermocoagulated cases), followed by carcinoma *in situ* (15.55%) and atypical metaplasia (12.5%, only represented by CIN I lesions).

We examined then the CIN III behaviour after therapy, taking into account at the same time the cyto-histological type and the performed treatment (tab. 4).

Atypical metaplasia appears to heal after any type of treatment; only a case, treated by conization, presented a recurrence as CIN I lesion.

Severe dysplasia and carcinoma *in situ* have similar behaviours; the former, however, presents a higher number of persistences (no CIN III lesions) and recurrences, mostly due to diathermocoagulation.

As to surgical treatments, hysterectomy achieves more healing than conization (81.96% versus 69.44%), but the difference is not significant.

Persistences and recurrences appear also following hysterectomy and may depend on CIN mostly multicentric origin and vaginal involvement.

As we already said, we controlled the cases of recurrence periodically at 6, 12, 18, 24 mo., 3, 5, 10 y.rs.

In this way we could note that the recurrence rate is high during the first twelve months after treatment (40%), and then decreases as time passes, without becoming null even after 10 years (fig. 1).

We then performed "transversal measurements" on the patients with recurrence, and gained fictitious cohorts which indicate the behaviour in the ten post-treatment years (tab. 5).

The results are expressed in fig. 2. The highest recurrence-rate occurs in the first year, while it is halved in the second

Table 6. — *CIN III diagnostic schedule.*

Suggested investigations:	
— Colpocytology:	– cervical canal – portio – vaginal walls
— Colposcopy:	– cervical canal – portio – vaginal walls
— Sight-biopsy:	– cervical canal – portio – vaginal walls

Table 7. — *Scheme of post treatment follow-up in CIN III.*

Suggested investigations:	year	periodicity
— Colpocytology	I	– 3 months
+	II	– 6 months
— Colposcopy	III	– 6 months
	following	– 1 year

one, and then decreases towards a steady level of about 13-15%, which is however higher than in healthy women.

DISCUSSION

The results of our study on the behaviour in time of CIN grade III after the treatment, point out that surgery ensures the higher healing-rate, whether hysterectomy or conization are performed, while diathermocoagulation seems unsatisfactory.

Conization has the advantage of confirming or disproving the diagnosis of non-invasion before hysterectomy, even if a careful pre-surgical diagnosis mostly coincides with the post-surgical one; in the few cases in which they differ, we have to face microcarcinomas which can be properly treated also by simple hysterectomy.

The choice between the two types of operation will then be based on other parameters, such as the age or the simultaneous presence of a gynecological disease requiring hysterectomy.

The number of persistences and recurrences is high (24.82%) even after surgery; however, it might be further lowered if the type of operation were decided only after a careful diagnosis of the lesion extension, localization and cytohistological type.

In fact any grade of CIN and its precursors can extensively affect the portio with the involvement, sometimes, of the fornices, and even be placed in the vaginal walls which can also be their only localization.

Colposcopy, colpocytology and sight biopsies of the cervical canal, portio and vagina (tab. 6), which give us a precise lesion-map, are then essential investigations to make the subsequent treatment a truly radical one.

To obtain a complete healing the type of operation is, in fact, negligible: it is the removal or lysis of every endocervical, esocervical or vaginal region where CIN is located, no matter its grade, that is indispensable.

Sight surgical therapy on the lesion-map will probably lead to eliminate persistences but some recurrences will continue to occur.

So high a recurrence incidence, suggests to consider these patients as a high-risk group for CIN reappearance even many years after the operation.

The persistence of this risk could be due to the persistence of the inducing factors, and to the intrinsic features of the CIN lesion, which may rise from different areas, not only simultaneously but also in different times.

A very close monitoring of these patients (tab. 7) seems required in the first year after surgery, when we observed the highest rate of persistences and recurrences, while, subsequently, their incidence decreases as time passes by.

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