

# USE OF B.C.G. AS LOCO-REGIONAL ASPECIFIC IMMUNOSTIMULATOR IN CERVICAL CARCINOMA

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## SUMMARY

This study concerns the possible use of BCG in oncologic gynecology for loco regional stimulation or loco aspecific active immunotherapy.

The Authors administered BCG into the portio of 45 women affected by cervical cancer (stage I and stage II) immediately after the cytohistologic diagnosis and 21 days before the surgical intervention.

The Authors conclude that the submucosal inoculation of BCG into the portio causes hyperplastic reactions in this area and in the loco-regional lymphatic system with stimulation of the T-lymphocytes and with production of Interferon. Anyway this stimulation has a limited duration.

The use of BCG in the aspecific immunotherapy of malignant tumours has already been thoroughly discussed in the literature (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22) and therefore needs no further confirming. Furthermore, BCG, applied in the sub-clinic phase of the disease, is regarded by many as the ideal drug for an adjuvant therapy before surgical treatment, thanks to the lack of significant side-effects. Indeed, the use of the antitubercotic vaccine can produce nothing more than moderate fever, light regional lymphadenopathy or arthralgia lasting just a few days.

This study analyses the possible use of BCG in oncologic gynecology for loco-regional stimulation or loco-regional aspecific active immunotherapy immediately after the cytohistologic diagnosis of malignant neoplasia has been reached, that is before the real operatory intervention.

The scope of this first study has been confined to cervical tumours. First of all, we have carefully evaluated the BCG dose to be inoculated into the portio to avert the risk of local or general unpleasant side-effects. We have finally assessed whether the BCG-induced immunologic stimulation has lasting effects and put forward pathogenetic hypotheses.

## MATERIAL AND METHODS

Our study concerned 45 women affected by cervical cancer (stage I or II). They had previously undergone PPD and their skin response had been absent, slight (+) or moderate (++).

We used the BCG of the "Istituto Vaccinogeno Antituberculare". 0.10 ml of vaccine were administered to patients with + or ++ PPD. Patients with +++ PPD response were excluded. The solution was injected into the portio under the mucosa and radially, to the four cardinal points. Surgical interventions were scheduled at 21 days from the BCG inoculation.

No reaction was observed to the BCG inoculation and laparotomy did not show anything in the peritoneum or abdominal organs. Only a few lymphnodes, particularly obturatory, grew slightly.

The operation was carried through regularly and lymphadenectomy raised no particular prob-

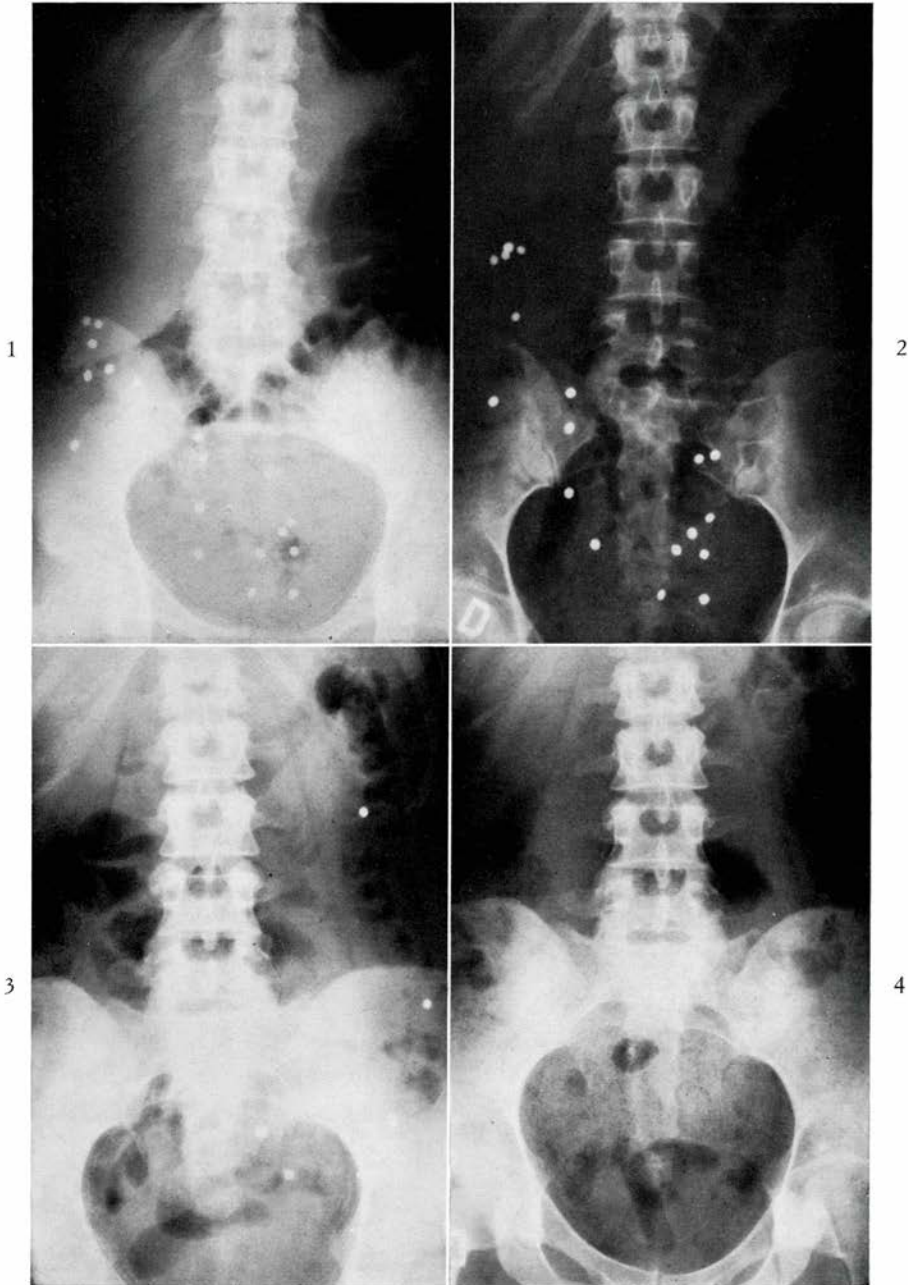


Fig. 1. — Lymphnode with well circumscribed focus including a giant Langhans cell. In the peripheral area, the lymphatic tissue shows marked activation of the paracortical area with isolated immunoblasts. Fig. 2. — Lymphnode showing evident activation of T-dependent zones, rich in immunoblasts. Fig. 3. — Lymphnode with marginal sinus presenting metastasis. Paracortical area with venular hyperplasia and high density of immunoblasts. Fig. 4. — Same as fig. 3; enlargement.

lem. No complication appeared in the post-operative period.

In the first year following the intervention, three patients were re-operated due to benign abdominal lesions. They underwent biopsy of the paraaortic lymphnodes. The operated patients, at the level of the uterine cervix, presented granulomatous infiltration with disseminated, sometimes confluent foci, mainly of elementary tuberculum structure, but without caseation.

The metastasis-free lymphnodes presented marks of marked sinus histiocytosis associated with follicular hyperplasia. Some of them presented small isolated granulomatous nidi without Langhans cells (fig. 1).

The hyperplasia of the paracortical area, with activation of the reticular elements and many immunoblasts, is a very characteristic factor. The germinal centers as well are activated and mitosis, macrophages and lymphoid cells can be observed (fig. 2).

All lymphnodes, including the pararectal and paraaortic ones, are involved. Furthermore, post-capillary venules, whose endothelium is often prominent, show evident hyperplasia.

The lymphnode with initial metastasis in periferal sinus shows marked activation of the T-dependent area with large amounts of lymphocytes and, above all, immunoblasts (figs. 3, 4). The re-operated patients' lymphnodes do not show the activation of the T-dependent zone that is usually observed after BCG and that was previously observed in the pelvic lymphnodes of these same patients.

## DISCUSSION

This study shows that the sub-mucosal inoculation of BCG into the portio triggers off productive hyperplastic reactions both in this very area, with activation of immunocompetent elements, and in the loco-regional lymphatic system with stimulation of the activity of the T-lymphocytes governing cellular immunity.

At lymphnodal level, the follicular structure is altered from the very beginning by the occurrence, in the sinus, of a rather intense histiocytary reaction with follicular and paracortical hyperplasia resulting in the transformation of lymphocytes into immunoblasts. This form of immunity is linked to the presence of immunoblasts in the T-dependent area. In 1981, Ghione stated that adjuvants, like BCG, which have so far been used empirically,

produce the suitable conditions for the production of Interferon in loco. It is worth noting that this immunocompetent activation also occurs in lymphnodes with initial metastases. According to Tosi and Coll. (21), survival is directly proportional to the intensity of response in the sinus paracortical area. If this is so, not only is this treatment useful but can also be applied more frequently to stimulate the immunitary response of satellite lymphnodes, which is the first and perhaps the most important barrier to the diffusion of cancer.

The stimulation, however, has a limited duration since it could not be observed in the lymphnodes of the patients who were re-operated after one year.

The likely occurrence of immunodepression is therefore to be taken into account.

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