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# Effect of alkylglycerols on the frequency of fistulas following radiation therapy

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**Abstract.** The incidence of injuries following radiation therapy for carcinoma of the uterine cervix is markedly decreased by the administration of alkylglycerols. This is the case for less harmful injuries as well as for the more severe ones, i. e. the fistulas between bladder and vagina and between rectum and vagina, respectively. The most dramatic results were observed for injuries which resulted from a combination of radiation damage and residual and/or recurrent tumor growth in case alkylglycerols were administered in a prophylactic manner, i.e. before as well as during the period of therapy.

## Introduction

The aim with the present study has been to investigate whether or not alkylglycerols administered before and during (in a prophylactic manner) or only during (in a non-prophylactic manner) influence the incidence of injuries following radiotherapy for carcinoma of the uterine cervix. Problems connected with the development of radiation tissue damage following radiotherapy have earlier been elucidated in several publications from the Radiumhemmet in Stockholm, where all patients included in the present study received their treatment (3, 4, 5, 7, 8, 9).

## Material and Methods

The clinical experiments in this study have been conducted using alkylglycerol preparations from the liver oil of the Greenland shark. The preparation, produced by AB Astra with the working name AT 18, is a concentrate containing 85 per cent free alkylglycerols.

The alkylglycerols were administered orally in capsules, 2 capsules 3 times a day, each capsule containing 0.1 g of alkylglycerols. The total daily dosage thus amounted to 0.6 g.

The series of cases with invasive carcinoma of the uterine cervix, treated at the Department of Gynecology, Radiumhemmet, Stockholm, were reviewed during various periods. The patients were allotted to one of the following groups:

- I. Patients given alkylglycerols "prophylactically": i. e. during 7 days before and during the treatment period, as well as for 1–3 months after the completion of radiotherapy.
- II. Patients given alkylglycerols only during the period of radiotherapy and for 1–3 months thereafter, "non-prophylactic" administration.
- III. Patients given radiotherapy solely.

Groups I, II and III cases were studied during the time period 1963 – 1966. 99 per cent of the patients, treated for carcinoma of the uterine cervix during the period January 1, 1964 – February 15, 1966 received alkylglycerols either prophylactically or as non-prophylactic administration. These patients are enclosed in groups I and II. Patients within group III were treated during 1963 (348 patients) and February 16 – December 31, 1966 (309 patients). The patients have been followed for more than 5 years from the initiation of therapy.

The treatment was, in almost all cases, initiated with intracavitary radium application followed by external radiotherapy. For data regarding radiation treatment the reader is referred to previously published reports (5, 6).

In the calculation of the incidence of radiation injuries in the bladder, rectum, ureters, and small intestine the principles given by Kottmeier and Gray and Joelsson and Bäckström have been used in this investigation (9, 10, 11).

In earlier follow-up studies, regard has only been paid to injuries due to the radiation treatment itself (R-injuries). In this study, however, the injuries due to the combination of radiation tissue damage and residual and/or recurrent tumor growth have been classified as complex injuries (C-injuries) and have been considered in addition. The sum of the injuries (R-injuries + C-injuries) is defined as the total number of injuries (I-injuries).

The injuries have been classified according to the following schedule defined by Kottmeier (9):

- |           |                                                                                                                                                                                                                                            |
|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade I   | Injuries producing mild subjective symptoms accompanied by minimal objective changes in the mucosa of the organ. These injuries are considered as <i>radiation reactions</i> rather than real injuries and have consequently been omitted. |
| Grade II  | Injuries which are composed of moderately to severe objective changes, such as areas of necrosis, ulcers or moderate stenosis.                                                                                                             |
| Grade III | Bladder and ureter injuries comprising fistulas, and rectal and intestinal injuries comprising stenoses of such an extent that colostomy has been required.                                                                                |
| Grade IV  | Rectal and intestinal fistulas.                                                                                                                                                                                                            |

Injuries which appear within three months of treatment have been excluded, and those injuries which are not clearly related to the radiation treatment or to tumor growth have also been omitted. Only the injuries which appear within 5 years after the onset of radiation treatment have been taken into consideration in this investigation. Patients with complex injuries (C-injuries) have clinically detectable cancer, residual cancer or recurrent tumor growth, confirmed by biopsy or autopsy.



## Results

### Effect of alkylglycerols on the different grades of injuries.

As a supplement to the earlier presentations of the effect of alkylglycerols, (1, 2, 3) the effect of these agents on the different grades of pure radiation injuries and complex injuries has now been analyzed. (Figures 1 – 3). It is observed that:

1. The incidence of total grade II injuries (I-injuries, grade II) is 9 per cent in the prophylactic group and 24 per cent in the control group, i. e. a reduction with 60 per cent, Fig. 1.

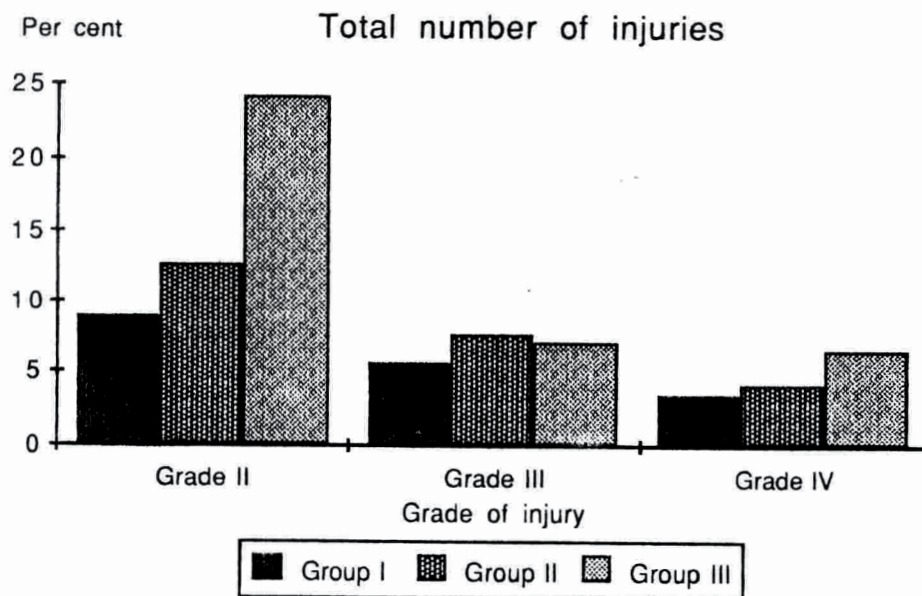


Figure 1. Total incidence of grade II, grade III and grade IV injuries in the groups with prophylactic administration of alkylglycerols (group I), non-prophylactic administration (group II), and no administration at all (group III).

2. The incidence of grade II radiation injuries (R-injuries, grade II) is considerably reduced while virtually no effect is observed on radiation injuries of grade III and IV, Fig. 2.
3. The complex injuries of all grades are markedly reduced, Fig. 3.

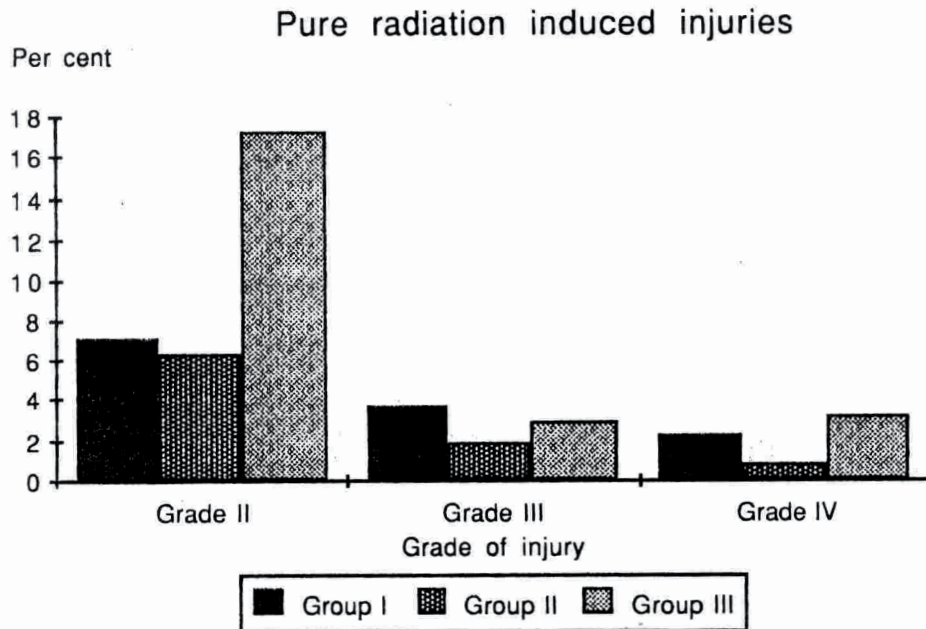


Figure 2. The incidence of pure radiation induced injuries of grade II, grade III and grade IV in the groups of patients with prophylactic administration of alkylglycerols (group I), non-prophylactic administration (group II), and no administration at all (group III).

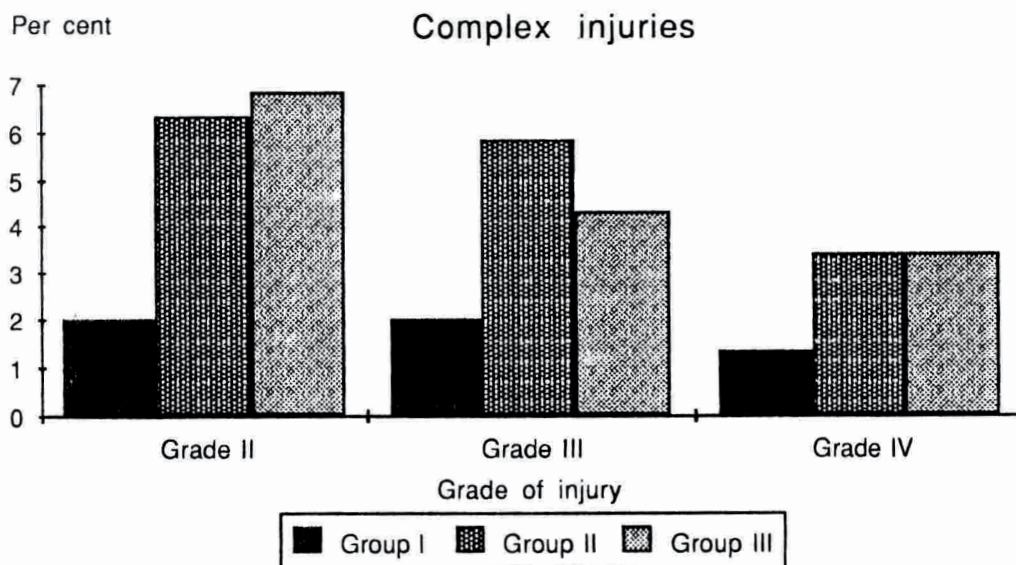


Figure 3. The incidence of complex injuries of grade II, grade III and grade IV (injuries as a combination of radiation tissue damage and residual and/or recurrent tumor growth) in the groups of patients with prophylactic administration of alkylglycerols (group I), non-prophylactic administration (group II), and no administration at all (group III).

4. In the "non-prophylactic" group only the radiation injuries are reduced while the incidence of the complex injuries remain the same, Fig 2 and 3.

#### Incidence of fistulas following radiation therapy.

It is of special interest to study the effect of alkylglycerols on the incidence of fistulas following radiation therapy. Bladder injuries of grade III and rectal injuries of grade IV together constitute the fistulas. It is observed that:

1. The total number of fistulas (I-injuries grade III and IV, bladder and rectum) is considerably lower in the prophylactic group than in the control group (6.2 per cent compared with 11.6 per cent), Fig 4.
2. The fistulas belonging to the complex injury group (C-injuries grade III and IV, bladder and rectum) have a low figure of to 2.9 per cent compared with 7.3 per cent, Fig 4.
3. The pure radiation fistulas (R-injuries grade III and IV, bladder and rectum) but not the fistulas of complex origin are decreased in number in the non-prophylactic group, Fig 4.

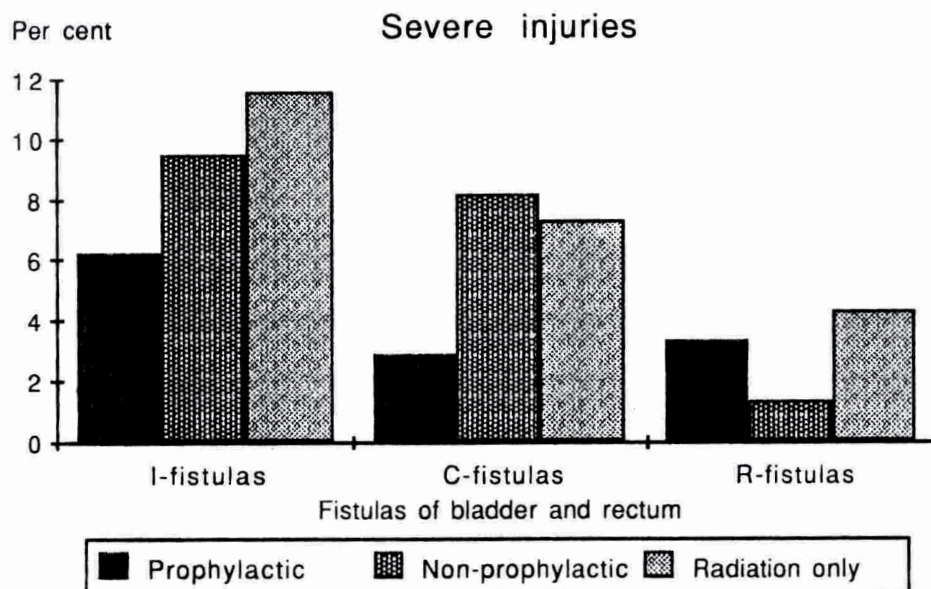


Figure 4. Severe injuries, i.e. fistulas of bladder and rectum in the three groups: total number of fistulas (I-fistulas), fistulas as a result of radiation injury and residual and/or recurrent tumor in combination (C-fistulas) and pure radiation induced fistulas (R-fistulas). Alkylglycerols were given in a prophylactic manner, nonprophylactically or not at all.



## Discussion

As there is always a certain degree of subjectivity in the interpretation of injuries following radiation treatment it has been considered of interest to analyze the effect of alkylglycerol treatment on the injuries divided by grade of severity as well as background of occurrence. Especial interest has been focused on the bladder injuries grade III and the rectal injuries grade IV, i. e. the fistulas – because an injury of this degree can not be misinterpreted. The result of the analysis shows that the effect of alkylglycerols on fistula formation is similar to the effect on injuries in general; a marked effect on the total incidence of fistulas with a greater effect on fistulas on the basis of radiation injury and verified tumor growth in combination (C) than on pure radiation fistulas (R).

It should be recalled that taking only radiation injuries (R) into consideration, these injuries are in most cases healed after a period of 6–12 months. Even if the radiation injuries are painful for the patient, they have only a marginal effect on the survival rate. Considering, on the other hand, patients with complex injuries, one faces a different situation: almost all of these patients are dead (98–100 %) within five years. These complex injuries are reduced to one third when alkylglycerols are given prophylactically in comparison with the patients who received radiation therapy solely.

Grade III bladder and grade IV rectal injuries constitute the fistulas. They are reduced from 11.6 per cent to 6.2 per cent by the prophylactic alkylglycerol administration, a decrease of 47 per cent. It is of importance to mention that the beneficial effect of alkylglycerols is observed not only for the less harmful radiation injuries (especially grade II) but also for the more severe injuries, the fistulas.

It has been demonstrated in earlier publications that alkylglycerols have several important effects in cancer therapy. Alkylglycerols prevent for example to some extent the leucopenia and trombocytopenia resulting of radiation (1). Furthermore, an inhibition of tumor growth and a decrease of the number of both radiation and complex injuries are observed when alkylglycerols have been administered prior to radiation treatment of patients with cancer of the uterine cervix. In this paper it has especially been stressed that the fistulas have been markedly reduced by the prophylactic administration with alkylglycerols, which certainly proves to be of value as a complement to conventional radiation therapy in cancer treatment.

## References

1. Brohult A. Alkoxyglycerols and their use in radiation treatment. *Acta Radiol*, Suppl 223, 1963.
2. Brohult A, Brohult J, Brohult S. Biochemical effects of alkoxyglycerols and their use in cancer therapy. *Acta Chem Scand* 1970;24:730.
3. Brohult A, Brohult J, Brohult S, Joelsson I. Effect of alkoxyglycerols on the frequency of injuries following radiation therapy for carcinoma of the uterine cervix. *Acta Obstet Gynecol Scand* 1977;4:441.
4. Gray MJ, Kottmeier HL. Rectal and bladder injuries following radium therapy for carcinoma of the cervix at Radiumhemmet. *Am J Obstet Gynecol* 1957;74:1294.
5. Joelsson I. Radiotherapy of carcinoma of the uterine cervix with special regard to external irradiation. *Acta Radiol*, Suppl 302, 1970.
6. Joelsson I, Bäckström A. Dose rate measurements in bladder and rectum. *Acta Radiol Ther Phys Biol* 1969;8:343.
7. Joelsson I, Räf L, Söderberg G. Stenosis of the small bowel as a complication in radiation therapy of carcinoma of the uterine cervix. *Acta Radiol Ther Phys Biol* 1971;10:593.
8. Brohult A, Brohult J, Brohult S, Joelsson I. Effect of alkoxyglycerols on the frequency of fistulas following radiation therapy for carcinoma of the uterine cervix.
9. Kottmeier HL. Carcinoma of the Female Genitalia. The Abraham Flexner Lectures, Series No. 11. The Williams & Wilkins Co., Baltimore, 1953.
10. Kottmeier HL, Gray MJ. Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix. A five year follow up. *Am J Obstet Gynecol* 1961;82:74.
11. Kottmeier HL. Complications following radiation therapy in carcinoma of the cervix and their treatment. *Am J Obstet Gynecol* 1964;88:854.