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REDUCED MORTALITY IN CANCER PATIENTS AFTER  
ADMINISTRATION OF ALKOXYGLYCEROLS

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**Abstract.** A regression of tumor growth is observed when alkoxyglycerols are administered prior to radiation treatment of patients suffering from cancer of the uterine cervix. This regression is remarkably higher for patients below the age of 60 years than for those over 60. The regression has been demonstrated by a change in the quotient between the incidence of early and advanced stages.

**Key words:** Alkoxyglycerols, alkylglycerols, shark liver oil

Alkoxyglycerols occur in small quantities in many natural products. In the hemopoietic organs of mammals, particularly the bone marrow, they are relatively abundant. They are also found in relatively high concentrations in human mother's milk. They occur most abundantly in nature in the liver oil of certain species of shark. The general formula for alkoxyglycerols is  $\text{CH}_2\text{OH}.\text{CHOH}.\text{CH}_2\text{O}.\text{R}$ , where R is a long-chain aliphatic radical.

The alkoxyglycerols have proved to be of medical interest (1–9). To some extent they prevent leukopenia and thrombocytopenia. The administration of alkoxyglycerols before, during and after radiation treatment of patients with cancer of the uterine cervix results in higher survival rates than if radiation treatment alone is given (1, 2, 3). Furthermore, the alkoxyglycerols promote the growth of *Lactobacillus lactis* (2), the formation of antibodies (5), and they reduce to a large extent (50%) the frequency of injuries following radiation therapy (6, 8, 14).

An investigation into the regression of tumor growth after administration of alkoxyglycerols prior to radiation treatment of patients suffering from cancer of the uterine cervix has been published earlier (9). The purpose of the present study was to investigate the influence of age on this regression.

## MATERIALS AND METHODS

The clinical experiments in this study were conducted using alkoxyglycerol preparations from liver oil of the Greenland shark. The preparation, produced by AB Astra with the working name AT 18, is a concentrate containing 85% free alkoxyglycerols. The contents of various alkoxyglycerols from a variety of sources are given in Table I.

The alkoxyglycerols were administered orally in capsules, two capsules three times a day, each capsule containing 0.1 g of alkoxyglycerols. Thus the total daily dose was 0.6 g.

The practical procedure was as follows. Immediately upon receipt of the referral letter, the patient was given a date for the commencement of radiotherapy and at the same time a package containing the alkoxyglycerols and information regarding dosage. At the start of the radiotherapy, the

Table I. Percentage composition (weight) of alkoxyglycerols from various sources.

Alkoxyglycerols	Human bone marrow	Human milk	Liver oil: Greenland shark
14:0			2.0
15 <sup>a</sup>			0.7
16:0	29.4	23.9	9.1
16:1		trace	10.8 <sup>b</sup>
17	7.6	3.6	3.6
18:0	24.6	22.8	2.8
18:1	16.7	33.8	59.4 <sup>b</sup>
18:2		1.4	1.6
18:3			
19 <sup>a</sup>	6.1	2.4	1.5
20:0	2.9	1.6	
20:1	3.2	2.3	6.2
22:0	0.7	0.7	
22:1	5.1	3.4	2.2
24		2.1	

Analyses are according to Hallgren & Larsson (2, 3). The number of carbon atoms in the first column refers to the long-chain component of the molecule. The number after the colon denotes the number of double bonds.

<sup>a</sup>Both branched and normal chains C<sub>15</sub>, C<sub>17</sub> and C<sub>19</sub> are present.

<sup>b</sup>Greenland shark liver oil contains 3–4% methoxy-substituted alkoxyglycerols (12, 13)

Table II. Definitions of clinical stages.

<i>E: Early stages</i>	
Stage I	Carcinoma strictly confined to the cervix
Stage I A	Cases of early stromal invasion
Stage I B	All other cases of stage I
Stage II A	The carcinoma extending beyond the cervix but not extending onto the pelvic wall. The carcinoma involves the vagina, but not the lower third. No parametrial involvement
<i>A: Advanced stages</i>	
Stage II B	The carcinoma extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina, but not the lower third. Parametrial involvement
Stage III	The carcinoma has extended onto the pelvic wall. On rectal examination there is no cancer-free space between the tumour and the pelvic wall. The tumour involves the lower third of the vagina
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum

Definitions according to FIGO (International Federation of Gynecology and Obstetric)

period of medication and the administration schedule were noted in the case report.

The entire series of cases with invasive carcinoma of the uterine cervix, treated at the Department of Gynaecology, Radiumhemmet, Stockholm, during the period 1958–75, was subsequently reviewed. The patients comprised all stages (Table II) and were allotted to the following groups.

#### Group I

Those who adhered to the scheme of prophylactic alkoxyglycerol medication, i.e. took alkoxyglycerols for 7 days before radiotherapy, during the radiation treatment, and for 1–3 months after the completion of therapy.

*Period 1.* From September 1, 1964 to February 15, 1966, the majority of the patients (458) had taken alkoxyglycerols prophylactically.

*Period 2.* A double-blind study comprising 137 patients was conducted, 1970–73. This is the second prophylactic group.

*Period 3.* During the years 1973–75 every second patient was given alkoxyglycerols 'prophylactically' (245). The cases were chosen at random.

#### Group II

Group II comprised all those who were given radiotherapy without any prophylactic administration of alkoxyglycerols, i.e. all patients who had not received alkoxyglycerols prior to radiation treatment.

## RESULTS

### Distribution of stages

The distribution according to clinical stage for all patients during the period 1958–75 is given in Table III. The C patients (C = controls) did not receive any prophylactic alkoxyglycerols, while the P patients did receive such prophylactic medication. The decrease in advanced stages after prophylactic administration was statistically significant ( $p < 0.001$ ). The results of this work have been discussed in an earlier publication (9).

### Dependence of age

It has been argued that the shift in stage after administration of alkoxyglycerols could possibly be due to an unequal distribution of the age of the patients with the passage of time. We therefore found it desirable to consider the influence of age on the stage distribution. The results are given in Table IV, where the patients have been divided into four age groups ( $> 60$ ,  $51–60$ ,  $41–50$ ,  $\leq 40$  years). The change in the stage distribution with age is remarkable, both for the control groups (C) and for the prophylactic groups (P). For the control group over 60, the proportion of early

Table III. Distribution according to clinical stage (1958–75).

	I A	I B	II A	II B	III	IV	I–IV	E	A	E/A
C										
n	374	1 044	1 215	888	609	274	4 404	2 633	1 771	1.49
%	8.5	23.7	27.6	20.2	13.8	6.2		59.8	40.2	
P										
n	77	282	245	125	82	30	841	604	237	2.55
%	9.2	33.5	29.1	14.8	9.8	3.6		71.8	28.2	

C: Controls (radiotherapy); P: Prophylactic administration of alkoxyglycerols; E: Early stages E = I A + I B + II A; A: Advanced stages A = II B + III + IV



Table IV. Distribution according to clinical stage (1958–75); association with age.

Age Group	≤40		41–50		51–60		>60	
	C	P	C	P	C	P	C	P
<b>I A</b>								
n	103	19	171	31	58	20	42	7
%	11.1	12.7	12.2	11.6	5.2	9.2	4.4	3.4
<b>I B</b>								
n	354	75	376	110	209	67	105	30
%	38.0	50.0	26.9	41.0	18.8	30.9	11.0	14.6
<b>II A</b>								
n	283	38	366	75	304	73	262	59
%	30.4	25.3	26.1	28.0	27.3	33.6	27.4	28.6
<b>II B</b>								
n	99	12	271	29	286	33	232	51
%	10.6	8.0	19.4	10.8	25.7	15.2	24.2	24.8
<b>III</b>								
n	65	4	155	17	171	21	218	40
%	7.0	2.7	11.1	6.3	15.4	9.7	22.8	19.4
<b>IV</b>								
n	28	2	61	6	86	3	99	19
%	3.0	1.3	4.4	2.2	7.7	1.4	10.3	9.2
<b>I–IV</b>								
n	932	150	1400	268	1114	217	958	206
<b>E</b>								
n	740	132	913	216	571	160	409	96
%	79.4	88.0	65.2	80.6	51.3	73.7	42.7	46.6
<b>A</b>								
n	192	18	486	52	543	57	549	110
%	20.6	12.0	34.8	19.4	48.7	26.3	57.3	53.4
<b>E/A</b>								
Quotient	3.85	7.33	1.87	4.15	1.05	2.81	0.75	0.87

C: Controls (radiotherapy); P: Prophylactic administration of alkoxyglycerols; E: Early stages E = I A + I B + II A; A: Advanced stages A = II B + III + IV

stages (E) is 43%, increasing to 79% for the age group under 40.

A decrease in advanced stages (A) is observed for the four prophylactic groups due to administration of alkoxyglycerols prior to radiation treatment. The change in the stage distribution with age is consequently greater for the prophylactic groups than for the control groups.

#### Stage distribution and mortality

The decrease in advanced stages is bound to influence the mortality following radiation treatment. In Table V the figures are given for patients who died within 5 years, for the four groups. In Table VI we have summarized the figures for early and advanced stages in order to compare the results. If the decrease in advanced stages and corresponding increase in early

stages are correct, we must find a lower percentage of deceased patients ( $D_A$ ) for the advanced stages in P groups with prophylactic administration of alkoxyglycerols than in the control groups (C), and for the early stages a higher percentage of deceased patients ( $D_E$ ). This is distinctly the case. The overall decrease in deceased patients ( $D_T$ ) is mainly due to the decrease in advanced stages, since the mortality rate is higher for the advanced than for the early stages. All our results indicate very strongly that the shift in stages is correct, and we consider that we have produced conclusive evidence that regression of tumor growth occurs after administration of alkoxyglycerols. From Tables V and VI and Fig. 1 and 2 it follows that the mortality for advanced stages is remarkably lower for patients under 60 years of age than for patients over 60. This is valid for the prophylactic

Table V. Deceased patients for the clinical stages (1958–75); association with age.

Age Group	≤40		41–50		51–60		>60	
	C	P	C	P	C	P	C	P
I A/D								
n	—	—	6	—	1	1	6	—
%	—	—	0.4	—	0.1	0.5	0.6	—
II B/D								
n	44	10	55	13	40	8	29	5
%	4.7	6.7	3.9	4.9	3.6	3.7	3.0	2.4
II A/D								
n	93	13	94	21	99	20	91	25
%	10.0	8.7	6.7	7.8	8.9	9.2	9.5	12.1
II B/D								
n	60	6	127	15	148	15	137	25
%	6.4	4.0	9.1	5.6	13.3	6.9	14.3	12.1
III/D								
n	51	1	120	16	122	13	167	28
%	5.5	0.7	8.6	6.0	11.0	6.0	17.4	13.6
IV/D								
n	25	2	58	5	77	3	94	16
%	2.7	1.3	4.1	1.9	6.9	1.4	9.8	7.8
I–IV								
n	932	150	1 400	268	1 114	217	958	206
E/D								
n	137	23	155	34	140	29	126	30
%	14.7	15.3	11.1	12.7	12.6	13.4	13.2	14.6
A/D								
n	136	9	305	36	347	31	398	69
%	14.6	6.0	21.8	13.4	31.2	14.3	41.5	33.5

D: Deceased within 5 years; N: Total patients in the group; P: Prophylactic administration of alkoxyglycerols; E: Early stages

E = I A + I B + II A; A: Advanced stages A = II B + III + IV

Table VI. Stages and mortality; association with age.

Group	No. of patients	A		D <sub>total</sub>		D <sub>E</sub>		D <sub>A</sub>		Age
		n	%	n	%	n	%	n	%	
C	958	549	57.3	524	54.7	126	13.2	398	41.5	>60
P	206	110	53.4	99	48.1	30	14.6	69	33.5	
C–P			3.9		6.6		–1.4		8.0	
C	1 114	543	48.7	487	43.7	140	12.6	347	31.2	51–60
P	217	57	26.3	60	27.6	29	13.4	31	14.3	
C–P			22.4		16.1		–0.8		16.9	
C	1 400	486	34.8	460	32.9	155	11.1	305	21.8	41–50
P	268	52	19.4	70	26.1	34	12.7	36	13.4	
C–P			15.4		6.8		–1.6		8.4	
C	932	192	20.6	273	29.3	137	14.7	136	14.6	≤40
P	150	18	12.0	32	21.3	23	15.3	9	6.0	
C–P			8.6		8.0		–0.6		8.6	
C	4 404	1 770	40.2	1 744	39.6	558	12.7	1 186	26.9	All ages
P	841	237	28.2	261	31.0	116	13.8	145	17.2	
C–P			12.0		8.6		–1.1		9.7	

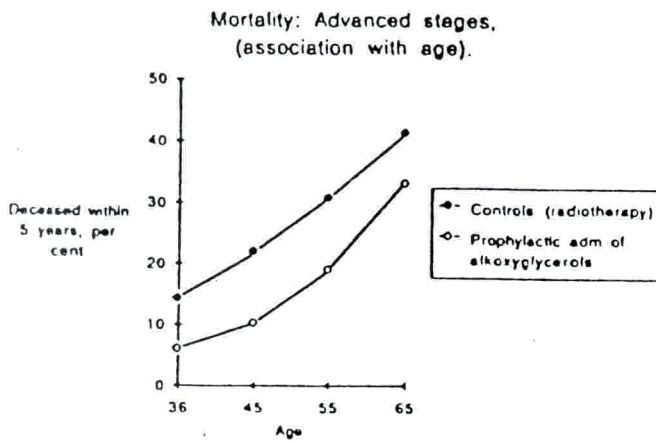


Fig. 1. Mortality of patients in advanced stages, association with age.

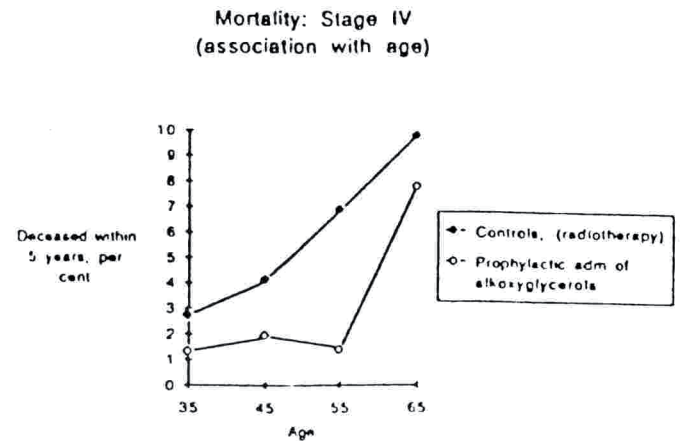


Fig. 2. Mortality of patients in stage IV, association with age.

groups as well as for the control groups. By contrast, the mortality for early stages is constant for all age groups, for prophylactic as well as for the control groups.

For a study of the regression of the different advanced stages (IIB, III and IV) it is desirable to compare one group including all patients under 60 with the group of patients over 60. The results are given in Table VII, where R is the relative decrease in deceased patients in comparison with the control groups. For patients under 60, the decrease is nearly 50% when all advanced stages are taken into consideration, and 65% for stage IV alone.

### Different effects of alkoxyglycerol administration

#### 1. Administration during radiation treatment

To some extent, alkoxyglycerols prevent leukopenia and thrombocytopenia (2) as a result of radiation. The incidence of radiation injuries was considerably lower when alkoxyglycerols had been administered during the radiation treatment (8).

#### 2. Administration before commencing radiation treatment

A decrease in advanced stages was observed when alkoxyglycerols were given prior to radiation treatment, and was followed by a decrease in mortality (Table V), an effect which was expected.

Table VII. Comparison of patients >60 vs. <60 years of age.

Age group	<60				>60			
	C	P	C-P	R	C	P	C-P	R
No. of Pat	3446	635			958	206		
D <sub>T</sub>								
n	1220	162			524	99		
%	35.4	25.5	9.9		54.7	48.1	6.6	
D <sub>E</sub>								
n	432	86			126	30		
%	12.5	13.5	-1.0		13.2	14.6	-1.4	
D <sub>A</sub>								
n	788	76			398	69		
%	22.9	12.0	10.9	48	41.5	33.5	8.0	19
D <sub>IIB</sub>								
n	335	36			137	25		
%	9.7	5.7	4.0	41	14.3	12.1	2.2	15
D <sub>III</sub>								
n	293	30			167	28		
%	8.5	4.7	3.8	45	17.4	13.6	3.8	22
D <sub>IV</sub>								
n	160	10			94	16		
%	4.6	1.6	3.0	65	9.8	7.8	2.0	20

R: Relative decrease in per cent of deceased patients in comparison with the control groups:  $(R = (D_C D_P) / D_C \times 100)$



Table VIII. Total deceased patients ( $D_T$ ) and percentage of early stages (E).

Age	C		P	
	DT%	E%	DT%	E%
> 60	54.7	42.7	48.1	46.6
51-60	43.7	51.3	27.6	73.7
41-50	32.9	65.2	26.1	80.6
≤ 40	29.3	79.4	21.3	88.0
All ages	12.7	100	13.8	100

The patients who received alkoxyglycerols prior to radiation were also given alkoxyglycerols throughout the radiation period (2-3 months). Did this comparatively long period of administration of alkoxyglycerols have any effect on the mortality, or was the decrease in mortality due solely to the shift in stages which occurs before the start of the radiation treatment?

In order to elucidate the question, overall mortality ( $D_T$ ) has been studied as a function of the distribution of the early stages (E) and the advanced stages (A). It must be pointed out that the study concerns only any possible effect of alkoxyglycerols during the radiation period once the distribution of stages has been determined.

In Table VIII the total of deceased patients ( $D_T$ ) and E have been collected from Tables IV, V and VI for the control groups (C) as well as for the prophylactic groups (P), which had received alkoxyglycerols before and during radiation treatment. For a presentation of the variation in  $D_T$  with the stage distribution either E or A can be used as a variable ( $E + A = 100$  in all cases).

The variation in  $D_T$  with E is shown in Fig. 3, both for the control groups (C) and for the prophylactic groups (P) which had received alkoxyglycerols before and during the radiation treatment.  $D_T$  as a function of E is the same for the control as for the prophylactic groups. No further decrease in mortality ( $D_T$ ) was observed for the alkoxyglycerol group vis-à-vis the control group. It is only the decrease in advanced stages, a result of the administration of alkoxyglycerols before the radiation treatment, which has any effect on the mortality.

## DISCUSSION

### Natural substance

It is noteworthy that the reduced mortality was observed following administration of

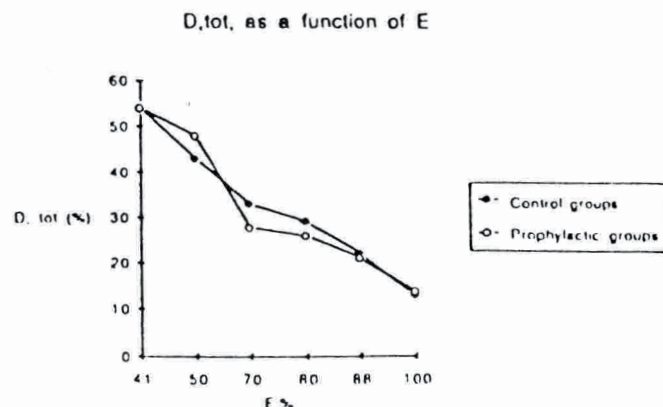


Fig. 3. Total deceased patients ( $D_T$ ) as a function of the early stages (E).

stance, alkoxyglycerols, found in the human body. To our knowledge it is the first time that such a result has been reported. As pointed out earlier, alkoxyglycerols occur mainly in the bone marrow and in mother's milk.

From table VI it follows that the decrease in the advanced stages is followed by a decrease in deceased patients following radiation treatment. The number of metastases and complex injuries (7, 8) due to the treatment also decreases after the administration of alkoxyglycerols — which is to be expected, since they occur more frequently in advanced stages than in early stages.

### Why tumor regression of advanced stages?

Reduced mortality is observed only for advanced stages. It would be of great interest to find an explanation (or at least a kind of hypothesis). If we assume that there is a reaction between the alkoxyglycerols and a substance in the tumor cell (or membrane) and that this reaction results in a destruction of the tumor cells, the effect should first be observed for the advanced stages where the carcinoma has extended beyond the cervix.

### Inhibition of tumor regression by irradiation

If alkoxyglycerols are given only during the radiation period, no decrease in deceased patients or in the number of metastases and of complex injuries will be observed, as in the case where alkoxyglycerols were given before the treatment (7, 8). The cell (or cell-membrane) is partly destroyed by the radiation, and therefore one explanation for the lack of effect might be that no interaction with alkoxyglycerols can take

# Alkoxyglycerols in the future?

The first positive effects of alkoxyglycerols were published about 30 years ago (for reference, see 2). A decreased mortality after administration of alkoxyglycerols was reported in *Nature* 1962 (1), and in the 1960s and 1970s three series of experiments were carried out, with positive results (3, 8, 9). The association of age with the decrease in advanced stages has given more support to the importance of these non-toxic substances, which is a reason why they should be more used in cancer therapy in the future.

## SUMMARY

1. The change in the stage distribution with age is remarkable both for the control groups and for the prophylactic groups. The early stages (E) increased particularly in the age groups below 60 years.
2. A decrease in advanced stages (A) after administration of alkoxyglycerols is observed for all ages, especially for the age groups below 60 years.
3. The decrease in mortality is due mainly to the decrease in advanced stages.
4. The mortality for advanced stages is considerably lower for patients below 60 years. This is valid for the prophylactic and for the control groups, whereas the mortality for early stages is constant for all age groups, for the prophylactic and for the control groups.

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