THE EFFECT OF SCALP TOURNIQUET USE ON ALOPECIA IN CANCER CHEMOTHERAPY

By

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CHAPTER I.

INTRODUCTION

Statement of the Problem

Loss of scalp hair is a common side effect in cancer chemotherapy. The resulting partial or total baldness often creates a difficult psychological burden for the patient in an already distressing clinical situation. To minimize alopecia, the use of a scalp tourniquet to occlude the blood supply to hair follicles has been advocated by some clinicians, primarily by word of mouth, during the past ten years. Others have tried it and given up, stating that it did not seem effective. Still others have never given it a trial, stating that theoretically it did not seem possible, or that patients were unconcerned about alopecia. If it can be shown that scalp tourniquets are effective, patients can easily be spared additional suffering by the use of this simple maneuver at the time of chemotherapy.

Review of the Literature

There have apparently been only four references to scalp tourniquet use in the medical literature. The first two appeared simultaneously in two letters to the editor of the British Medical

Journal in 1966. Simister (1966) stated, "Occlusion of the blood supply to the scalp during and for five minutes after injection of a potentially epilating drug will, according to several unpublished reports, prevent or reduce to insignificant proportions the incidence and extent of hair loss. A special narrow sphygmomanometer cuff for scalp occlusion is applied before the injection and inflated to a pressure above systolic, which is maintained until five minutes after the injection" (p. 1138).

On the same page is a letter to the editor from Hennessey (1966): "For the past twelve months I have been using an inflatable tourniquet around the head, pumped up to 10 mm. Hg. above the systolic pressure immediately before the injection is given and kept so for five minutes. There continues to be some hair loss, but I have had no instances of complete alopecia since." (The drug to which he is referring here is cyclophosphamide.) He stated that if alopecia occurred in patients receiving intraperitoneal Thio-tepa, "it would not be reasonable to maintain scalp ischaemia to the degree I have used it for intravenous therapy for a sufficient length of time. Partial ischaemia might be maintained, however, for a longer period, perhaps 3-4 hours, by asking the patient to wear a rather tight-fitting bathing cap . . ." (p. 1138).

In 1970, in a letter to the editor of the New England Journal of Medicine in which reference was made to the British communication, a pediatric group at Yale stated that, "Alopecia after vincristine can be markedly reduced by the scalp tourniquet. We have used the scalp tourniquet concomitantly with Vinblastine and

Actinomycin-D therapy, but have not treated sufficient numbers of patients to state unequivocally that it is of benefit. It has not been effective in protecting against cyclophosphamide-induced alopecia" (O'Brian et al., 1970, p. 1469).

Also in 1970, Binns and Southall (1970) stated in an article about intensive cyclophosphamide therapy, "The use of a pneumatic head cuff during and immediately after injection was not successful in preventing hair loss with the dosages that were used, and complete hair loss was usual, in about three weeks" (p. 546).

Two recent articles written by nurses called attention to scalp tourniquet use. Marino and Harris (1975, p. 32) recommended it with the intravenous alkylating agents, plant alkaloids, and the antibiotics, stating that "much of hair loss can be prevented by using a scalp tourniquet." In their experience, the tourniquets should be left in place for 10 to 15 minutes as the intravenous drug is being given. They stated that sudden hair loss was more devastating to a patient's self-image than gradual hair loss, as he had more time in the latter case to prepare his family and friends for the change. Apparently they believed that scalp tourniquet use slowed down the rate of hair loss as well as reducing or preventing it.

In an article about Hodgkin's Disease, Keaveny (1975, p. 78) wrote, " . . . promising have been efforts to prevent or reduce hair loss by applying a large, soft rubber tourniquet around the forehead for 10 to 15 minutes following the administration of intravenous drugs. I have one young man who has prevented significant

hair loss despite a prolonged course of chemotherapy by using a tourniquet."

These few evaluations of scalp tourniquet experience in the literature appear to be highly impressionistic. Either no controlled studies have been undertaken, or they have not been reported due to negative results.

Scientific Background

Two issues appear to be involved in approaching this problem: first, the viability of the rationale for scalp tourniquet use, and second, the feasibility of testing its efficacy.

"The rationale for the use of the scalp tourniquet was that the (drugs) are rapidly cleared from the blood stream after intravenous injection, presumably because of tissue fixation of the drug. Since the scalp is supplied by superficial blood vessels that can be temporarily occluded by pressure, the contact of the drug with hair follicles can be minimized" (O'Brian et al., 1970, p. 1469). Theoretically, then, it is necessary to examine the nature of the hair growth, the effects of cancer chemotherapy on hair growth, the scalp blood supply, and the pharmacokinetics of the drugs, in order to assess the viability of the rationale.

The hair growth cycle

Van Scott (1968) gave an excellent review of the hair growth cycle. During the period when hair growth prevails, it occurs at a steady pace from day to day. Each follicle has a bulbous base of mitotically active pluripotential matrix cells, the growth and

differentiation of which give rise to all the cells of the hair shaft. From the matrix, cells move up in rows to the upper bulb and elongate vertically. Continued growth then forces the hair upward finally to emerge on the skin surface. Matrix cells have no diurnal rhythm. Not even starvation depresses their mitotic activity (Montagna, 1974). In man, the doubling time of these cells is 23 hours, an exceptionally high rate among body tissues. It is active not only in terms of the high proportion of cells undergoing mitosis per day, but also in the extreme speed with which these mitoses are completed.

But growth does not continue indefinitely. At intervals, mitosis stops abruptly and completely, the hair root undergoes orderly involution and enters a state of dormancy. At the end of the dormant period, which lasts for approximately three months in man, the old hair is shed, a new hair root is regenerated, and growth of a new hair begun. The period of hair growth is known as the stage of "anagen," the period of involution as "catagen," and the period of dormancy as "telogen." Catagen lasts for only a few days, while the length of anagen in man is fairly uniform for all the scalp follicles of an individual, and in the average person the growth of a hair from a follicle will continue for approximately three years.

The first, the shortest, and the only hair growth cycle in synchrony occurs in utero in man. After birth, the cycle moves to a state of mosaicism where each follicle follows its own cycle of anagen-telogen, independent of other follicles. In the normal

adult scalp approximately 90% of the follicles are in the anagen phase of the cycle, 10% are in telogen, and less than 1% are in catagen. Hair on other parts of the body has a much shorter period of anagen appropriate to its length. Hairs on the arm, for instance, are in anagen phase for only three months at a time.

The effects of cancer chemotherapy on hair growth

The drugs used in cancer chemotherapy affect cells which are dividing rapidly and this includes not only the target malignant cells but the normal cells of the bone marrow, gastro-intestinal epithelium, and hair follicles which are highly mitotically active. Van Scott (1968) and Levantine and Almeyda (1973) have reviewed these effects on human hair. Regardless of its site of action or mechanism of action, each drug interferes with hair growth by effectively blocking at one step or another the mitotic cycle of the germinative hair matrix cells. Small doses of the drugs decrease the size of the hair bulb, the keratogenous zone, or both, leading to constriction in the hair shaft. The constriction moves distally as the hair grows. Even where a larger dose has caused the hair bulb to atrophy completely it is reversible if the drug is stopped. Clinically evident hair loss resulting from these drugs may occur in two ways. Hairs with atrophied roots are readily lost, either by falling out spontaneously or after a casual disturbance such as combing the hair. Hairs with marked constriction of the shaft, on the other hand, break off easily at the point of constriction, producing the characteristic anagen alopecia. The

root, however, remains in the scalp, since it has already recovered from the trauma of the drug and has produced the hair shaft containing the constriction (Crouse & Van Scott, 1960).

Hair root damage to patients treated for cancer is usually not recognized until alopecia develops. Patients often do not begin to notice hair loss until several weeks after treatment because although hair fall usually begins one to two weeks after treatment is initiated, it takes six to eight weeks of increased loss before the 25% hair loss necessary to produce clinically evident alopecia is reached (Levantine & Almeyda, 1973).

With X-rays, acute effects occur in the hair root similar to those described above for the cancer drugs. In addition, most hair roots so affected enter a stage of telogen, and, provided the dose of radiation has not been so large as to prevent growth entirely, regrowth of hair is delayed until the onset of the next anagen phase which occurs three months later. It should be kept in mind that the effects of X-irradiation are local, and affect hair growth only when given therapeutically to the head for a condition such as a brain tumor.

Effects of agents which interfere with mitotic generation of cells can, of course, be clinically manifest only in growing hairs, those in anagen. Loss of eyebrows, pubic and axillary hair is usually not seen in patients receiving chemotherapy because most of the hair follicles in these regions are in the dormant phase, telogen. Also, patients never experience complete scalp epilation because of the 10% of telogen hairs which are unaffected by the drugs.

The Neoplastic process itself does not appear to affect hair proportions or hair roots (Crouse & Van Scott, 1960).

The scalp blood supply

The hair follicles receive an abundant blood supply, the main sources of which are situated in the subcutaneous tissues. The internal carotid artery supplies those arteries servicing the frontal region, while the external carotid takes care of those vascularizing the rest of the scalp. Two branches of the external carotid, the posterior auricular and the occipital, course posteriorly to supply the area behind the ear and the back of the neck and scalp. The external carotid terminates by dividing into the superficial temporal and maxillary branches. The superficial temporal artery supplies the area in front of the ear and the side of the head. The internal carotid artery enters the skull through the carotid canal within the temporal bone, where it gives rise to the ophthalmic artery. The ophthalmic artery supplies all the structures in the bony orbit and sends twigs to the front of the scalp (Gray, 1972).

Therefore, it appears that the scalp is supplied with arteries which are superficial and could be occluded with external pressure. The fact that the internal carotid supplies the front of the scalp from the inside does not appear to present a problem as the ophthalmic artery comes out at the eye socket and sends twigs to the scalp which course up and over the cranium.

The blood supply to the head is relatively constant (as opposed to that of the skeletal muscles, which varies greatly with need).

After an intravenous drug is injected into a superficial vein in the arm, it courses through the heart and lungs, where the blood is oxygenated, subsequently flowing via the arteries to either head or trunk in a matter of a few seconds.

The scalp is considered a part of the skin. The metabolic rate of the cells of the skin is so low, especially if their temperature falls (as it does when the circulation is cut off), that permanent damage (necrosis) does not result until after many hours of complete ischemia (Burton, 1972). Therefore, it would seem that the hair follicles would be more damaged by chemotherapy than by the effects of scalp tourniquet occlusion. A scalp tourniquet could theoretically be left in place for a longer period of time than the five to fifteen minutes reported in the literature.

Pharmacokinetics of the drugs

There are approximately fifty different drugs used in cancer chemotherapy, and although they all interfere with DNA synthesis, they do not all have the same characteristics. (See Table 1 for the characteristics of the eight major drugs that are used in this study.) Not all of these drugs are cleared rapidly from the plasma by tissue-binding. Cyclophosphamide, a notorious epilator, is not activated until metabolized by the liver and then has a biological half-life of 6.5 hours. Methotrexate has a half-life of 12 hours. Adriamycin, although evidently rapidly tissue-bound, is still in the blood stream 27 hours after injection. It is true that one of the first anti-cancer drugs, nitrogen mustard, is very rapidly

Table 1

Pharmacologic Characteristics of Selected Anticancer Drugs

Drug	Cell Cycle Phase Specificity	Plasma $T_{1/2}$	Plasma Protein Binding	Entry Into CNS	Biotransformation		Main Route of Excretion
					Activation	Degradation	
Alkylating Agent							
Cyclophosphamide	NS	6.5 hr.	10%	Moderate	Oxidized by hepatic microsomal enzymes to biologically active and inactive products		Renal
Antimetabolites							
Methotrexate	S	12 hr.	50%	Minimal	None	None	Renal
6-Mercaptopurine	S	90 min.	10-20%	Moderate	To nucleotide	Oxidation to 6-thiouric acid	Renal
Cytosine Arabinoside	S	2 hr.	Negligible	Moderate	To nucleotide	Deamination to uracil arabinoside	Renal
5-Fluorouracil	NS	20 min.	?Negligible	Extensive	To nucleotide	Extensive	Lung & Renal
Vinca Alkaloids							
Vincristine	S	A few minutes	?Negligible	?Negligible	?Extensive		Bile
Antibiotics							
Dactinomycin	NS	A few minutes	?Negligible	Low	None	None	Bile
Adriamycin	NS	27 hrs.	Extensive	?Negligible	Extensive biotransformation to active and inactive metabolites		Bile

Abbreviation:
S-Phase-specific NS-Phase-non-specific CNS-Central nervous system $T_{1/2}$-Half-time of plasma clearance
?-Undetermined or estimated from known properties of the drug or a closely related drug
(Adapted in part from Cline-1975, p. 29)

tissue-bound and cleared from the blood, but it does not cause alopecia, presumably because it is so rapidly tissue-bound that it does not have time to reach the hair follicles. Vincristine is also rapidly cleared from the blood, as is actinomycin-D.

Pharmacological research has primarily been concerned with the effects of these drugs on tumors, hence very little is known about the details of their effects on hair follicles. However, observations of patients reveal that some drugs are much more epilating than others, but whether this is related to half-life, tissue-binding rapidity, a propensity for localizing in epithelioid tissues or other factors is not clear. The cyclic or non-cyclic nature of the drugs does not appear to be a factor. On the other hand, alopecia has been shown to be dose-related (Crouse & Van Scott, 1960). Very puzzling is the fact that hair regrowth after epilation often begins at approximately 3½ months from beginning of treatment regardless of the fact that chemotherapy continues unabated.

Empirically, applying the scalp tourniquet at the time when plasma drug levels are at their peak and leaving it in place as long as possible would appear to afford maximum hair follicle protection.

The way each drug is administered affects scalp tourniquet use and potential effectiveness. Drugs that are given by intravenous bolus injections achieve immediate peak plasma levels and then taper off according to first-order kinetics. (Figure 1.) In this instance the scalp tourniquet would appear to be more effective when used as described in the literature, with inflation to above systolic blood pressure during drug administration and several minutes thereafter up to 15 minutes.

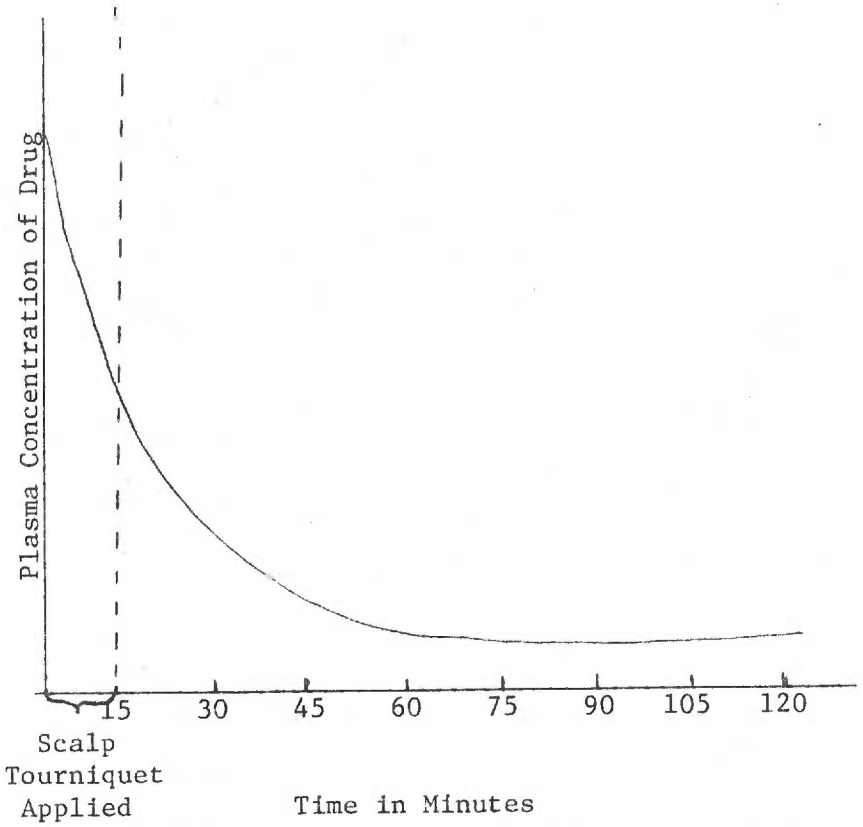


Figure 1

Theoretical Plasma Levels Over Time After Drug Administered by Intravenous Bolus

When the drug is given by infusion, i.e., dilution with D_5W and administered over a period of time, hair follicle protection is more difficult to achieve. It is not possible to leave the scalp tourniquet in place for more than about twenty minutes as it becomes too uncomfortable for the wearer. Since peak plasma levels are slower to be reached with infusion, it seems reasonable to apply the tourniquet when plasma levels are highest, during the last ten minutes of the infusion and the ten minutes immediately thereafter. (Figure 2.)

However, this model for scalp tourniquet use with infusions poses significant problems, primarily because the blood level of the drug has already risen before the occlusion would stop blood flow. That blood may then lie stagnant in the scalp and follicles may be exposed to the drug in the stagnant blood. On the other hand, the active form of Cytoxan (the only drug infused in this study) may not be present in the blood for ten to fifteen minutes after injection because it must first be metabolized by the liver (Table I).

To effectively deal with this question experimentally, drugs and metabolite blood concentrations would have to be measured with time. This was not possible for this study. Given the problems clinically, it seemed best to use the tourniquet when plasma levels were highest.

Feasibility of Testing the Hypothesis

The preceding review of the literature provides sufficient theoretical rationale for predicting that the application of a scalp tourniquet during chemotherapy for cancer may inhibit hair

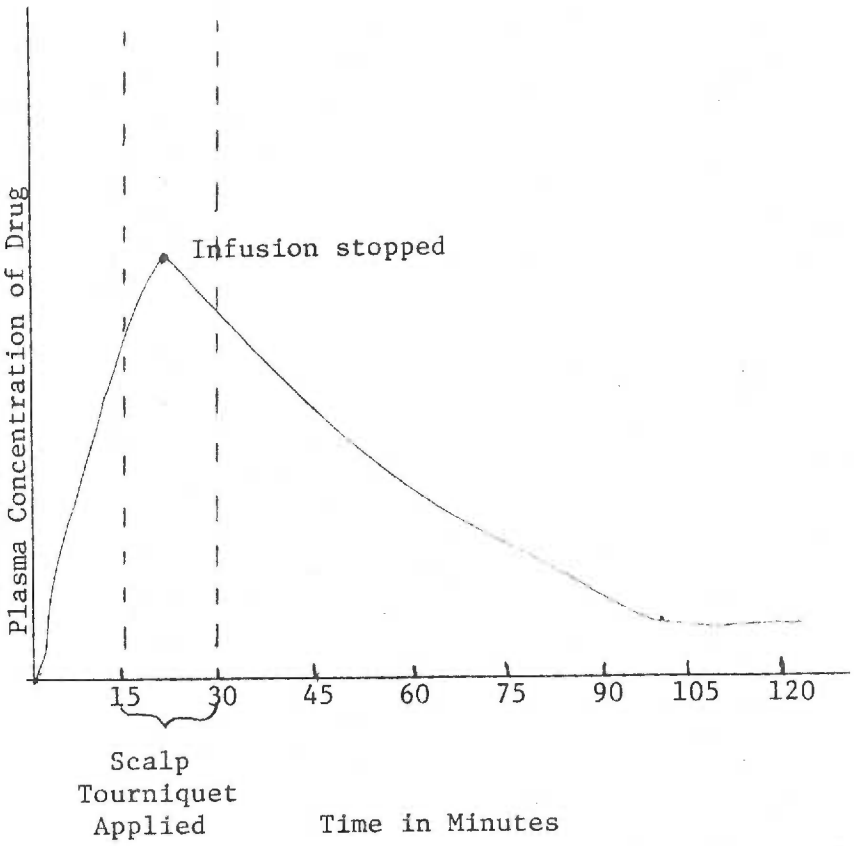


Figure 2

Theoretical Plasma Levels Over Time After Drug Administered by Intravenous Infusion

loss. However, a second issue must still be addressed; namely, the feasibility of testing the tourniquet's effectiveness given the contingencies of modern treatment procedures.

Some patients appear to be more prone to alopecia than others. Crouse and Van Scott (1960: pp. 86 and 88) present two tables, one showing the comparative effects of differing doses of Methotrexate on scalp hair, oral musosa, and bone marrow, and the other showing the comparative effects of drugs other than Methotrexate on the same parameters. These tables show that some patients experience more hair loss than others. " . . .Whether the hair changes, when apparent, were associated with the drugs, the specific disease, or unknown factors is not apparent" (p. 89). A claim for the effectiveness of a scalp tourniquet in reducing epilation in a specific patient would have to be tempered with the recognition that he might not have experienced alopecia if the tourniquet had <u>not</u> been used.

Cancer chemotherapy use has changed greatly over the past few years. Several years ago it would have been possible to study the relationship of a single drug to alopecia and scalp tourniquet use. Since drugs are currently given in very complex combinations, it is difficult if not impossible to separate out the individual drug kinetics from the total combined effect. The known characteristics of Vincristine, for instance, would appear to make this drug a good candidate for scalp tourniquet intervention, as pointed out by O'Brian et al. (1970). However, Vincristine today is almost never used as a single agent. It is used in many different combinations to induce remissions in leukemias, lymphomas, myelomas, and some solid tumors.

There are more than one hundred different kinds of malignancies. For the treatment of each malignancy there exists a variety of chemotherapeutic regimes from which the clinician may choose. It is difficult to find more than one or two patients on a given protocol at any one time at one institution. Also, especially in the case of the liquid tumors, dosages are frequently adjusted and readjusted over a period of time, so that no two patients receive exactly the same total dosage.

Possible adverse effects of tourniquet use should be mentioned. In patients with acute leukemia, where the ultimate objective of treatment is to destroy not only the malignant clone in the bone marrow but each leukemic cell in the blood, preventing the chemotherapeutic drugs from reaching the scalp blood could interfere with the treatment. Because leukemic cells are now known to "hide" in the cranium, and cause relapse later on, current management often calls for intra-thecal Methotrexate or brain irradiation. It is possible that this problem may preclude the safe use of scalp tourniquets in patients with liquid tumors. However, in mentioning this issue, O'Brian et al. (1970) stated, "We have not been impressed by any difference in remission rates . . ." in leukemic patients on whom they have used scalp tourniquets (p. 1496). A potentially similar problem occurs in patients with solid tumors where the primary cancer is known to metastasize to the brain, such as sometimes occurs in lung cancer. It might be imagined that preventing the drugs from reaching any part of the head might permit a metastatic area to enlarge. However, since the scalp tourniquet occludes

only the superficial scalp circulation and does not interfere with drug reaching the brain, scalp tourniquet use should not put the patient in jeopardy.

Individual patient comfort precludes the use of tourniquets for long periods of time. Since the circulation is occluded, the scalp becomes numb after about fifteen minutes. The researcher applied the tourniquet to her own head on several occasions, inflated to 120 mm. Hg. (10 mm. Hg. above her systolic blood pressure) for up to 30 minutes. There was no pain, dizziness, syncope, or headache, only the discomfort of having one's head tightly "squeezed."

What is the rationale for doing this study some ten years after scalp tourniquets had been in vogue? Many physicians and clinics had empirically tried scalp tourniquets and found them to be ineffective at that time. The investigator believed that a controlled study would be worthwhile now for the following reasons:

1. Two recent nursing articles (Marino, 1974: Keaveny, 1975) had advocated their use.
2. At least one Portland oncologist uses scalp tourniquets on all his chemotherapy patients with all the drugs, and claims they are effective (Ellerby, 1976).
3. In discussing the issue of scalp tourniquet effectiveness with nurses practicing in the field of oncology, it became evident that they were all confused by the conflicting opinions. However, they were keeping an open mind and hoping for proven effectiveness.
4. It was possible to secure one of the original scalp tourni quets from Baum & Co. used by the Yale pediatric group

that claimed initial success in 1970 (O'Brian et al.). Since all the more recent references were to soft rubber bands, it was felt that perhaps this special tourniquet would be more effective.

5. Finally, the investigator was beginning a nurse practitioner chemotherapy clinic and wanted to know, once and for all, whether it was worth the effort and patient discomfort to use the tourniquets on the patients she treated.

Purpose of the Study

An experimental study was designed to demonstrate the extent to which alopecia was slowed, reduced, or prevented by use of a scalp toruniquet during chemotherapy.

Hypothesis

Application of a scalp tourniquet will reduce the amount of hair loss if used during the period of highest plasma concentration with selected chemotherapeutic agents.

CHAPTER II

METHODOLOGY

The Setting

This study was conducted at the Veterans Administration Hospital at Portland, Oregon. The Hospital is a 600-bed facility serving a primarily male population. Patients with bronchogenic carcinoma are diagnosed and treated by the Respiratory Service which has 46 inpatient beds. Approximately 100 patients are diagnosed as having bronchogenic carcinoma each year. Of these, approximately half are treated with radiotherapy. The other half, those with more extensive disease, are treated with systemic chemotherapy. There is a lung cancer chemotherapy outpatient clinic on Thursday mornings where many of these patients come for their treatments, although most of the patients in this study were treated and followed in the nurse-practitioner chemotherapy clinic conducted by this investigator. Since she does not have time to care for all the patients herself, she particularly selected those in this study.

The Portland facility participates in a nationwide Veterans Administration research program with a standardized treatment program for lung cancer chemotherapy. When this study was planned in May and June of 1976, Protocol 14, which had four different drug arrangements, was in use across the country. In addition,

there was a local protocol called COCA*, used only at the Portland facility. The five possible treatment regimes which could have been chosen for each patient placed on chemotherapy were included in the proposal for this study. The choice among the five treatments was determined randomly by a nationwide Veterans Administration computer program.

The Subjects

The population from which the sample was drawn consisted of veterans who were about to be treated with chemotherapy for bronchogenic carcinoma. The typical subject in this population was male, a World War II veteran, aged 50 years or over, with a long history of cigarette smoking. His condition had been recently diagnosed with the malignancy having already metastasized to brain, bone, liver, or lymph nodes. Without treatment he had a chance of living only a few weeks or months. With treatment he might prolong his life for a somewhat longer period. (See Table 2.)

Excluded from the study were those patients with a Karnofsky activity scale rating below 70 as it was very unlikely that they would live to complete the three months of the study. (See Appendix C.)

Identification of Variables

Independent Variable: Scalp Tourniquet Use

A special scalp tourniquet consisting of a seamless dipped

*COCA is the acronym for the drugs Cyclophosphamide, Oncovin (Vincristine), Methotrexate, and Actinomycin-D. In reality it should be called COMA, but due to the devastating nature of advanced bronchogenic carcinoma, it was felt by the Respiratory Service Chief that changing the name to COCA would be more socially acceptable to patients and staff.

Table 2

Life Expectency of 79 Lung Cancer Patients Treated with Chemotherapy at Portland V.A.H. in 1974 and 1975

Number	Pathological Type	Range	Median	Mean
32	Small cell	½-13 months	6½ mo.	7 mo.
27	Squamous cell	¼-18 months	8 mo.	4½ mo.
15	Adenocarcinoma	½-26 months	12½ mo.	4 mo.
5	Large cell	1-3 months	1½ mo.	2½ mo.

latex bag that measures 2 inches by 20 inches and a sateen cuff 35 inches in length with Velcro tape closures was used. This was the type of tourniquet described in the literature reporting initial good results (O'Brian et al., 1970; Simister, 1966; Hennessey, 1966). It is still available from W. A. Baum & Co., Inc., Copaigue, New York, for $10.00.

The scalp tourniquet was inflated to 10 mm. Hg. above systolic blood pressure of the patients in the control group during peak plasma drug concentration at the time they received their chemotherapy.

Dependent Variable: Extent of hair loss

To document the extent of scalp hair loss, each patient in the study was photographed in the Medical Illustration Department of the Portland Veterans Administration Hospital before beginning chemotherapy, and subsequently at two-week intervals. Pictures were taken for three months, at which time maximum hair loss should have occurred. Five black-and-white photographs of the head were taken each time--front, back, two sides, and top. These photographs were mounted by the Medical Illustration Department on a single sheet of paper. They were kept in a locked file cabinet until the end of the study, at which time an independent panel of three judges was asked to decide on the extent of hair loss for each patient. The judges did this by comparing the photographs taken before, during, and after the three months. The judges rated the patient's hair status on a continuum of 100% to 0%, 100% being the

patient's own hair status before beginning chemotherapy, and 0% being complete epilation. (Figure 3.) The judges arrived at independent decisions for each set of photographs, and these were then averaged. In order to assess whether hair loss was slower with scalp tourniquet use, the panel rated each patient's hair loss for each interval set of pictures.

Design and Randomization

This study was experimental in design. The main focus of the study was the manipulation of the independent variable, scalp tourniquet application. The study was originally planned to include patients on five different chemotherapeutic regimes, as indicated in Figure 4. However, the protocol for the national study was changed, making it possible to implement only the local COCA portion of the design.

It soon became clear that only a small number of patients would be available for the study. Therefore, it was important to ensure that patients would be dispersed evenly in both experimental and control groups. It was planned that after a patient had been initially randomized by computer to one of the drug regime groups, he would be randomized again by the investigator for the scalp tourniquet study thusly: the first patient eligible was to be placed in the experimental or control group by a flip of the coin. If he fell into a control group, the second patient was to be automatically placed in experimental. If the first was experimental, the second patient would become the control. The third patient was again randomly assigned, with the fourth patient being placed in the opposite group.

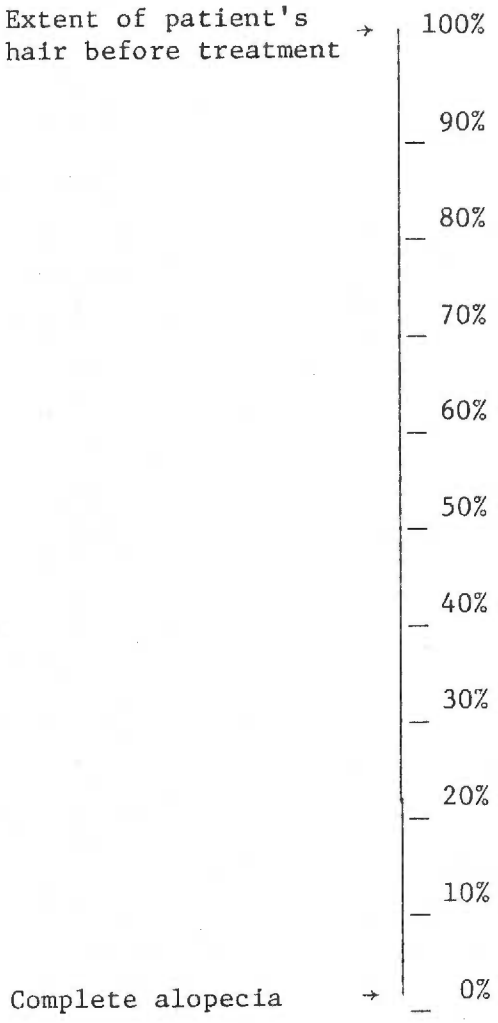
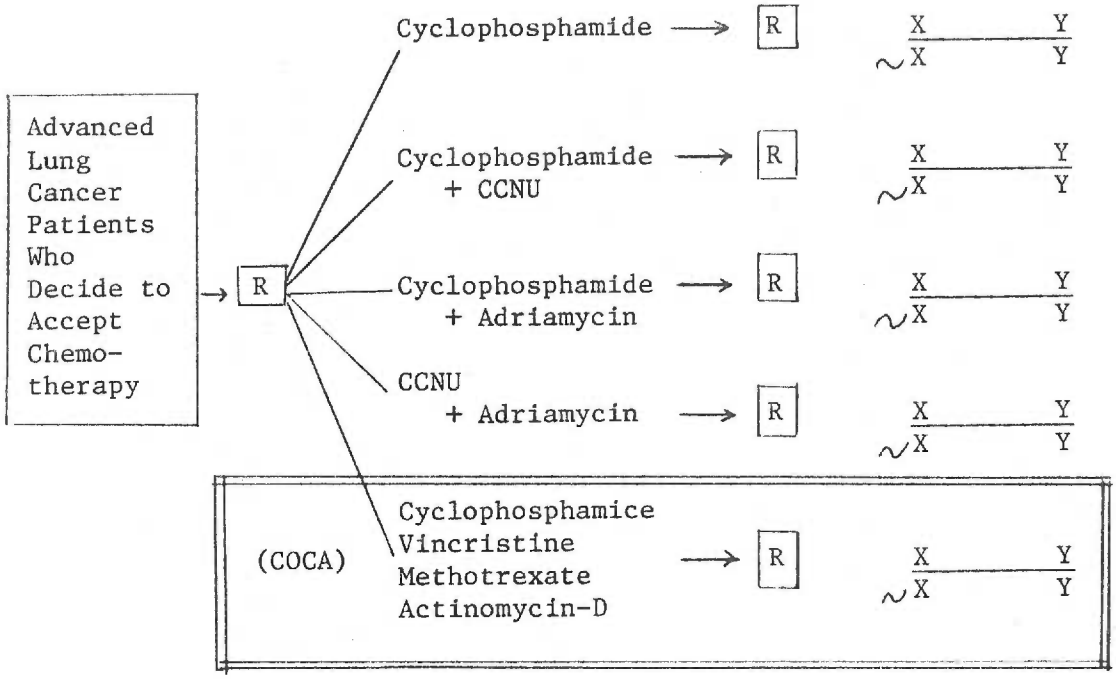


Figure 3

Continuum for Rating Retention of Scalp Hair by Patients Receiving Potentially Epilating Chemotherapy



R = Randomization
X = Scalp Tourniquet
~X = No scalp Tourniquet
Y = Hair loss

Figure 4

Original Study Design

There were some initial difficulties with the planned randomization that require explanation. The first COCA patient (#1, Table 7) was eligible for the protocol one week before the scalp tourniquet study was officially approved by the Human Subjects Committee of the Portland Veterans' Administration Hospital. Therefore, it was decided to make him a control without randomizing him.

A second patient who was eligible about a month later was assigned to the experimental group. However, he had received only one treatment when it was decided that he would receive concurrent brain irradiation, so he was dropped from this study. The third eligible patient should have been experimental, but he was very frightened at the prospect of the scalp tourniquet because of previous clotting problems. Since he did consent to be in the study as a control, and since there was a dearth of patients eligible and we did not wish to lose him, it was decided to put him in the control group out of turn. Also on that same day, another patient was started suddenly on COCA in the Clinic unbeknownst to the investigator. Again, we did not wish to lose him, so he was made a control also. At that point there were three control subjects only. Therefore, the next three patients were placed in the experimental group to even up the groups. The seventh patient became experimental by a flip of the coin, with the eighth then being control. The ninth patient was also properly randomized into the experimental group, and as it turned out, he was the last to receive COCA chemotherapy. In short, because of conditions beyond our control in the clinical situation, it was not possible to use the planned randomization.

However, this probably did not affect the results of the study, as there is no reason to believe that the members of one group, as finally constituted, had any greater natural tendency to be susceptible to hair loss than the members of the other group.

Procedure

The detailed procedure for this study with the COCA and Veterans' Administration Lung Group (VALG) Protocol 14 are outlined in Tables 3 through 6. (It should be noted that the VALG 14 regime involving Cytoxan alone was eliminated in May, 1976, because it proved to be least effective in controlling bronchogenic carcinoma.) Only the procedure in Table 3 was actually implemented. Each individual was studied for three months, as from clinical observation maximum hair loss occurs in that period of time in chemotherapy.

The scalp tourniquet research was planned to continue until 10 patients were accrued for each of the four regimes, giving 5 experimental patients and 5 control patients to be analyzed for each group. This would have given a total sample of 40 subjects.

The scalp tourniquet study was implemented in August, 1976. Two months later, the Veterans Administration Lung Group decided to phase out Protocol 14 in favor of a new regime, Protocol 16, which involved different drugs, including immunotherapy. Because of the difficulty in procuring the large quantities of the immunotherapeutic agent for a national study, there was a delay of almost a year in making the change. During this period only patients

Table 3

Procedure for COCA Group
(Two week intervals)

Group	Prestudy	TREATMENT												Post-Study
		Day 1		Day 15		Day 29		Day 43		Day 58		Day 71		
		Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	
Experimental	1. Sign Consent 2. Teach to use scalp tourniquet 3. Photos	Cyton. 40 mg/kg in 100 ml. D_5W-20 min. infusion	Inflate 10 mm. Hg. above systolic B.P. for last 10 min. of infusion & 10 min. after	Vincristine 2 mg. I.V. bolus Photos	Above systolic for 15 minutes	MTX 0.6 mg/kg. I.V. bolus Photos	Above systolic for 15 minutes	Actinomycin-D 2 mg. I.V. bolus Photos	Above systolic for 15 minutes	Cytox. 40 mg/kg in 100 D_5W-20 min. infusion Photos	Inflate 10 mmg. Hg. above systolic B.P. last 10 min. of infusion and 10 min. after	Vincristine 2 mg. I.V. bolus Photos	Above systolic for 15 minutes	Evaluation of Photographs by panel
Control	1. Sign Consent 2. Photos	Cytox. 40 mg/kg in 100 ml. D_5W-20 min. infusion	0	Vincristine 2 mg. I.V. bolus Photos	0	MTX 0.6 mg/kg I.V. bolus Photos	0	Actinomycin-D 2 mg. I.V. bolus Photos	0	Cytox. 40 mg/kg in 100 D_5W-20 min. infusion Photos	0	Vincristine 2 mg. I.V. bolus Photos	0	Evaluation of Photographs by panel

Table 4

Procedure for CCNU-Cytoxan Group (Eliminated October, 1976)
(Three week intervals)

Group	Prestudy	TREATMENT								Post-Study
		Day 1		Day 21		Day 42		Day 63		
		Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	
Experimental	1. Sign Consent 2. Teach to inflate scalp tourniquet 3. Photographs	CCNU 70 mg/m^2 p.o. Cytoxan 700 mg/m^2 I.V. infusion	Inflate 10 mm. Hg. above systolic last 10 min. & 10 min. after	Cytoxan 700 mg/m^2 I.V. infusion Photos	Inflate 10 mm. Hg. above systolic last 10 min. & 10 min. after	CCNU 70 mg/m^2 p.o. Cytoxan 700 mg/m^2 I.V. infusion Photos	Inflate 10 mm. Hg. above systolic last 10 min. & 10 min. thereafter	Cytoxan 700 mg/m^2 I.V. infusion Photos	Inflate above systolic for first 30 min.	Evaluation of Photos by panel
Control	1. Sign consent 2. Photographs	CCNU 70 mg/m^2 p.o. Cytoxan 700 mg/m^2 I.V. infusion	0	Cytoxan 700 mg/m^2 I.V. infusion Photos	0	CCNU 70 mg/m^2 p.o. Cytoxan 700 mg/m^2 I.V. infusion Photos	0	Cytoxan 700 mg/m^2 I.V. infusion Photos	0	Evaluation of Photos by panel

Table 5

Procedure for Adriamycin-Cytoxan Group (Eliminated October, 1976)
(Three week intervals)

Group	Prestudy	TREATMENT Day 1 Drug	Day 1 Scalp Tourn.	Day 21 Drug	Day 21 Scalp Tourn.	Day 42 Drug	Day 42 Scalp Tourn.	Day 63 Drug	Day 63 Scalp Tourn.	Post-Study
Experimental	1. Sign Consent 2. Teach to use scalp tourniquet 3. Photographs	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	Inflate 10 mm. Hg. above systolic last 10 min. & 10 after; release, repeat with 2nd infusion	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	Inflate 10 mm. Hg. above systolic last 10 min. & 10 after; release, repeat with 2nd infusion	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	Inflate 10 mm. Hg. above systolic last 10 min., & release, repeat for 2nd infusion	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	Inflate 10 mm. Hg. above systolic last 10 min. & 10 min. after, release, repeat	Evaluation of photos by panel
Control	1. Sign Consent 2. Photographs	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	0	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	0	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	0	Adriamycin 40 mg/m^2 I.V. infusion plus Cytoxan 700 mg/m^2 I.V. infusion	0	Evaluation of photos by panel

Photos | Photos | Photos | Photos

Table 6

Procedure for Adriamycin-CCNU Group (Eliminated October, 1976)
(Three week intervals)

Group	Prestudy	TREATMENT								Post-Study
		Day 1		Day 21		Day 42		Day 63		
		Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	Drug	Scalp Tourn.	
Experimental	1. Sign Consent 2. Teach to use scalp tourniquet 3. Photos	Adriamycin 40 mg/m^2 I.V. infusion CCNU 70 mg/m^2 p.o.	Inflate to 10 mm. Hg. above systolic for last 10 min. & 10 min. thereafter.	Adriamycin 40 mg/m^2 I.V. infusion Photos	Inflate to 10 mm. Hg. above systolic for last 10 min. & 10 min. thereafter.	Adriamycin 40 mg/m^2 I.V. infusion CCNU 70 mg/m^2 p.o. Photos	Inflate to 10 mm. Hg. above systolic for last 10 min. & 10 min. thereafter.	Adriamycin 40 mg/m^2 I.V. infusion Photos	Inflate to 10 mm. Hg above systolic for last 10 min. & 10 min. thereafter.	Evaluation of photos by panel
Control	1. Sign Consent 2. Photos	Adriamycin 40 mg/m^2 I.V. infusion CCNU 70 mg/m^2 p.o.	0	Adriamycin 40 mg/m^2 I.V. infusion Photos	0	Adriamycin 40 mg/m^2 I.V. infusion CCNU 70 mg/m^2 p.o. Photos	0	Adriamycin 40 mg/m^2 I.V. infusion Photos	0	Evaluation of photos by panel

starting on the COCA protocol were accepted into this study. There seemed to be no point in working with the others as there would not be sufficient numbers to evaluate, since the starting date of Protocol 16 was always held out to be so imminent.

In July, 1977, it was decided to close the COCA study which had been in effect since 1972. Therefore, subjects were no longer available for this study.

CHAPTER III

RESULTS AND DISCUSSION

During the 12 months of this study, only 9 patients met the criteria for admission into the study. Of these 9, there were five experimental patients and four control patients. Selected data on each patient are presented in Table 7, which shows that the two groups were essentially similar in age, tumor type, and extent of illness when they began. Of the nine patients in the sample, 7 died before the three-month period of the study of their hair loss could be completed. Therefore, the last photographs before their deaths were used for the final evaluation.

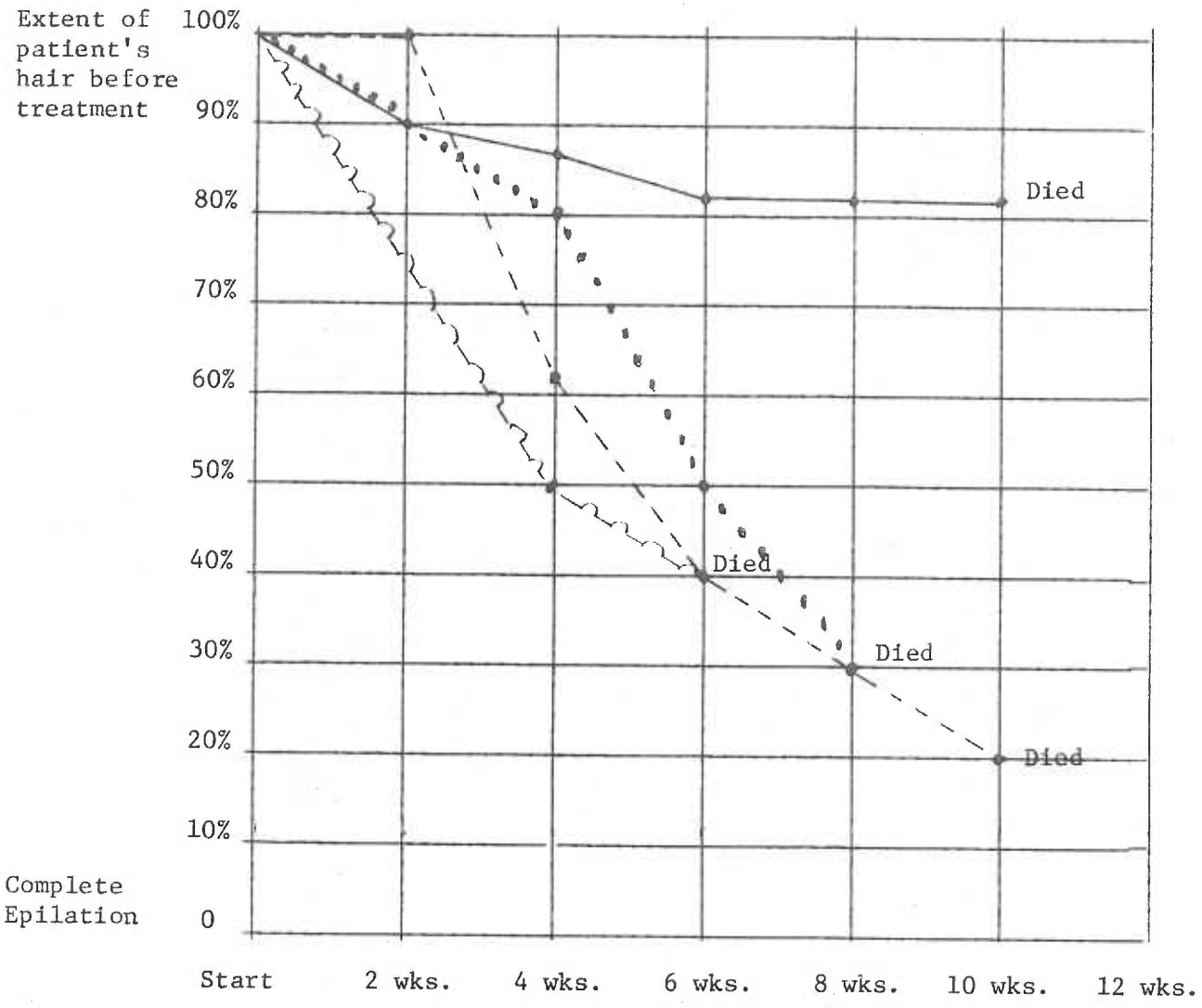
Three judges rated the set of photographs for each patient on a specially constructed graph similar to that used in Figures 5 and 6. (See Appendix E.) The three graphs for each patient were subsequently averaged by the investigator to give the composite for each patient shown in Figures 5 and 6. (Mean values for each group are presented in Table 8.) These figures show clearly the extent of hair loss for each patient over time. Given the pattern seen for the control group in Figure 5, and the experimental group in Figure 6, the significance of differences between these two independent groups was examined.

Because of the ordinal nature of the measurement used to quantify hair loss, the Mann-Whitney U test for non-parametric

Table 7

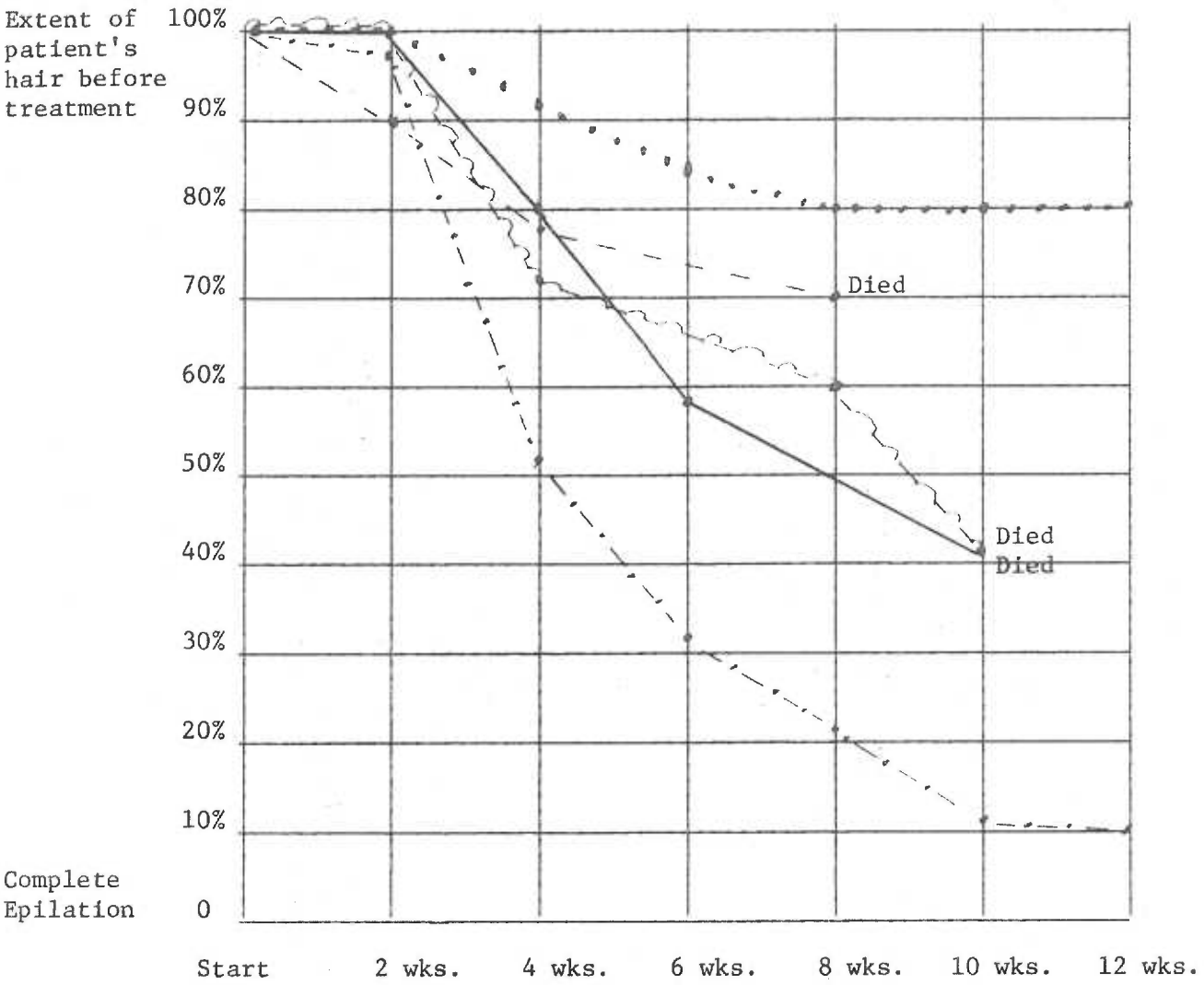
Selected Data on Patients in Scalp Tourniquet Study
(Numbers Reflect Time Sequence of Admission into Study)

Control Patient #	Age	Pathological Type	Date Started Study	Date Ended Study	Karnosfky at start	Doses During Study
1.	53	Adenocarcinoma	8-19-76	Died 11-5-76	70	Full
2.	69	Undetermined	10-13-76	Died 1-18-77	80	Full
3.	70	Squamous cell	10-13-76	Died 12-11-76	70	Full
7.	56	Squamous cell	3-10-77	Died 5-21-77	70	Full
Experimental Patient #						
4.	63	Oat Cell	10-28-76	Died 1-3-77	80	Full
5.	64	Adenocarcinoma	1-3-77	Died 3-4-77	80	Full
6.	80	Squamous cell	2-17-77	5-17-77	70	Full
8.	57	Squamous Cell	4-25-77	Died 7-11-77	90	Full
9.	61	Adenocarcinoma	5-5-77	8-5-77	70	Full



Loss of Scalp Hair by Control Group Patients
Receiving Potentially Epilating Chemotherapy
(without scalp tourniquet)

Figure 5



Patient # 4.

Patient # 5.

Patient # 6.

Patient # 8.

Patient # 9.

Loss of Scalp Hair by Experimental Group

Patients Receiving Potentially Epilating Chemotherapy

(with scalp tourniquet)

Figure 6

Table 8

Values for Hair Retention by Members of Experimental and Control Groups at Final Reading

Experimental (N = 5)	Control (N = 4)
80%	82%
70%	40%
43%	30%
43%	20%
10%	
Mean: 49.2%	Mean: 43%

data was selected for statistical analysis. The hypothesis stated that scalp tourniquet use would result in less alopecia than when not used. The computed value of the U was ≤ 8 which gave a probability of occurrence of .365 (Siegel, 1956). The difference between the control and experimental groups was therefore not significant, and the hypothesis was rejected. The scalp tourniquet was ineffective in preventing or reducing hair loss.

In addition to scalp tourniquet effectiveness in preventing or reducing hair loss, it was implied by Keaveny (1975) that scalp tourniquet use slowed down the rate of hair loss. Since photographs were taken of each patient at two week intervals, the judges were able to evaluate the hair loss of the patients over time as reflected in Figures 5 and 6. Inspection of these two figures reveals that the experimental patients did not lose their hair at a slower rate than did the control group patients. The statement by Levantine and Almeyda (1973) that hair loss begins at about two to two-and-a-half weeks and then progresses rather rapidly, was confirmed.

Discussion

The fact that all of the patients in the study were males should not compromise the external validity of the research design as hair follicles are apparently affected by chemotherapy on a non-sex, non-age basis (Van Scott et al., 1957). The fact that these men had less hair to begin with when treatment was instituted (because of shorter hair cuts and male balding patterns) than would women of comparable ages made quantification less difficult, as it

can be more readily seen photographicably when hair loss occurs. At least 25% alopecia is required before it becomes clinically evident.

Inasmuch as there were no dosage reductions in any of the patients due to leukopenia or thrombocytopenia during the time they were in the study, all the patients received identical amounts of drugs.

There were no apparent adverse effects from the use of the tourniquet.

The rationale for the use of a scalp tourniquet was that since drugs are rapidly cleared from the blood stream after intravenous injection and since the scalp circulation is supplied by superficial blood vessels that can be temporarily occluded by pressure, the chemotherapeutic drugs can be prevented from reaching the hair follicles by occlusion of the scalp blood supply by a special tourniquet at the time of intravenous injection. The hypothesis that use of the scalp tourniquet would prevent or reduce hair loss was rejected. There are probably two main reasons for this. First, the cytotoxic drugs may not all be rapidly cleared from the blood stream as originally thought and the drugs may not all be rapidly tissue-bound (Table 1). Secondly, the scalp circulation can only be occluded for a short period of time due to patient discomfort, consequently the hair follicles cannot be well-protected from durgs having a longer half-life or from drugs given by intravenous infusions.

This study was planned to address the use of the scalp tourniquet clinically as stated in the literature. The fact that patients cannot tolerate the tight occlusion for more than 20 minutes is a

definite limiting factor to using it for theoretical maximum effectiveness. Because of this, scalp tourniquet use has been based primarily on considerations of threshhold concentrations of the drug's effects on follicles, not duration of exposure. When scalp tourniquet use first appeared in the literature, it was believed that the drugs had very short durations of action and were rapidly tissue-bound. Today, with the plethora of new drugs and complex use of them, this appears to be no longer the case. It is true that the study design does not address issues of duration of exposure, but this is because clinically it is not possible to do so. In order to study the effect of time of exposure to the drugs on the hair follicles, the time course of the drug and its active metabolites in the scalp would have to be known. Since this could not be determined, the times chosen for the scalp occlusion with the tourniquet were based on the best available information about the plasma concentrations and half-lives of the durgs (Table 1).

The data reveal an interesting pattern of hair loss among these patients. Given the fact that they all received identical drugs under controlled conditions, one would expect them to all have rather comparable hair loss, which is not the case. By studying Figures 5 and 6, it can be observed that out of 4 or 5 patients, one will have almost total hair loss, one will have almost no hair loss, and the others will fall somewhere in between. Perhaps here we have the answer as to why some clinicians, such as Marino, Keaveny, and Ellerby, have continued to claim that scalp tourniquets were effective after they had fallen into disrepute in most

oncologic circles. If one applied a tourniquet to a group of patients with no controls, it may have appeared that retention of hair by some patients was due to the tourniquet.

Another reason that some clinicians have continued to use the tourniquet despite its questionable activity may lie in its psychological purpose. Patients undoubtedly feel comforted to know that everything possible is being done to help them. Scalp tourniquet use may also make the chemotherapy administrator feel better about his or her role, as it is difficult to give these drugs to patients knowing the devastating side effects they may produce.

The data, then, reveal that there are other than dose-related factors involved in whether a given patient will lose his hair or not. Speculation as to what these may be takes us back to the field of Dermatology.

It might be argued that a familial tendency to baldness predisposes some individuals but not others to hair loss. In rebuttal, the process of balding is not one of hair loss. Rather, male baldness is caused by the persistent reduction in size of scalp follicles from large to small. "Instead of formerly coarse and long scalp hairs, the new generations of hairs become finer and shorter. The condition is clearly associated with the androgen levels . . ." (Van Scott, 1968, p. 348). It might also be noted that in this study the patient who was most bald initially was one of those with almost no hair loss. There seems to be no correlation between the amount of hair each patient had before beginning chemotherapy and the amount he lost subsequently.

Although Montagna (1974) states that not even starvation depresses the mitotic activity of the hair follicle, there is some evidence that nutritional factors do in fact affect hair growth (Van Scott, 1974). It is known that many patients with advanced bronchogenic carcinoma have metabolic derangements leading to cachexia produced by the tumor itself. This is compounded by their poor nutritional intake due to anorexia and to the diversion of many dietary substances from normal use to support of tumor growth. However, since all the patients in this study were nutritionally depleted, it would be expected that any nutritional factors that were operating on hair growth would affect all of them.

It is know that certain dermatologic conditions are immunologically induced, although these are not well understood. Patients with advanced cancer receiving chemotherapy would be expected to have substantial immunological defects which might affect their hair. Again, however, one would suspect any such conditions to be seen more uniformly in all of the patients.

It must be kept in mind that the only parts of the hair follicle affected by chemotherapy are those mitotically active cells in the matrix which are in the anagen, or growth, phase. Is it possible that the two subjects with little hair loss had most of their hair follicles in the telogen, or resting, phase? If so, what could cause this diversion from normal? It is known that postpartum hair loss in the past, in many instances, was probably due to infection and fever inducing stress which caused conversion of large numbers of anagen hairs to telogen (Van Scott, 1968). Perhpas the two

patients with little hair loss in this study had sustained a similar major stress-producing event prior to starting chemotherapy. Even if it were the case that these two patients had endured some type of stress which put their hairs into telogen, they would have then been expected to lose most, if not all, of their hair after three months which did not in fact happen.

In pursuing the possibility that these patients had more than the average number of hairs in telogen (usually about 10%), two research reports from the Journal of Investigative Dermatology are of interest. Crouse and Van Scott (1960) found that the percentage of telogen hairs in 38 normal individuals ranged from 1% to 44%, with an average of 13.5%. Van Scott, Reinertson, and Steinmuller (1957), also examining normal subjects, reported that the proportion of telogen hairs ranged from 4% to 47%. The older subjects had more hairs in telogen than the younger subjects. However, when they examined the scalp hairs of patients with neoplastic diseases, the proportion of telogen hairs ranged from 2% to 76%, with the median and mean 8% and 33% respectively. The proportions of telogen hairs in cancer patients was greater than that found in normals. Therefore, it is possible that the two patients who retained their hair in this study, older men with advanced malignant disease, simply had a much greater proportion of their hairs in telogen than is normally seen. However, if this were the case, one would expect them to lose these telogen hairs in three months since that is the normal pattern of hair growth, unless the length of time of hairs in the telogen phase becomes more prolonged in these cases

as well. Had they lived, they could simply have been asked if they had needed to get their hair cut recently!

The most likely explanation for the differing patterns of hair loss observed in the patients in this study is that those with less hair loss had more hairs in telogen. This hypothesis could easily be confirmed. By using the microscopic examination of epilated scalped hair roots described by Crouse & Van Scott (1960) before beginning chemotherapy, the percentage of telogen hairs could be correlated with the extent of hair loss after treatments began.

Finally, the weaknesses of this study should be discussed. The major defect was the small sample size. Initially there was an attempt to include patients from other Veterans Administration Hospitals, but the change in Protocol 14 and the delay in starting Protocol 16 made this impossible. The COCA protocol was used only locally.

Although there were a few more patients than the 9 in this study randomized to the COCA group during the 11 months of this study, they were either receiving concurrent brain irradiation or had a Karnofsky Activity Scale below 70 which meant it was highly unlikely that they would live long enough to complete the study.

A second limitation involved the fact that 7 of the patients died before the study was completed. However, evaluation at two months is probably equally effective, as it appears that the main bulk of hair is lost during the first two months of treatment.

A third limitation involved having the photographs taken at each two week treatment interval. At times the photographer was

unavailable, and the pictures for that visit could not be taken.

A fourth weakness involved the judges' perceptions of hair loss as revealed in the photographs. Although the photos were large, clear, and showed hair detail quite well, slightly different lighting and angles may have made it difficult to get a perfectly accurate impression of hair loss. For instance, when one of the patients got a hair cut, one of the judges commented that it was difficult for her to separate the effects of the haircut from epilation due to chemotherapy. It should be added that the investigator particularly instructed the judges that not all patients receiving chemotherapy lose their hair, which many people believe to be true and was felt might bias their assessments. All things considered, given the alternatives of weighing hairs that had been shed or counting them, the pictures were quite satisfactory.

CHAPTER IV

SUMMARY AND CONCLUSIONS

Summary

The purpose of this study was to determine the effectiveness of a scalp tourniquet in preventing or reducing alopecia in patients undergoing cancer chemotherapy.

Using an experimental design, nine patients with a diagnosis of bronchogenic carcinoma at the Portland Veterans' Administration Hospital beginning on COCA chemotherapy were randomized to experimental and control groups. A scalp tourniquet was used on each patient in the experimental group for 15 or 20 minutes (depending on how the drug was administered) during the time of peak plasma drug concentration at each treatment. Photographs of the head were taken at two week intervals for each patient for three months (or until death) and were rated by judges at the termination of the study as to extent of hair loss.

Conclusions

Although it appears from this study that scalp tourniquet use may not be effective, the small sample size precludes any firm conclusions. The study involved only one combination of four drugs, given in specific sequence and time intervals. All the cytotoxic drugs behave differently, and are given in different intervals and sequences, which may affect hair losses differently than herein

stated. Two of the other notorious epilators, Adriamycin and Bleomycin, were not tested with the scalp tourniquet at all.

Very little prior research had been done into alopecia following chemotherapy. The present study sheds some new light onto this puzzling clinical situation. Although there are still many areas open to speculation, the door is now opened for further investigations which will ultimately benefit people with cancer.

Recommendations for Future Studies

Scalp tourniquet use could be tested with different drugs in a larger patient population.

Of more interest would be an investigation into the relationship between the percentages of anagen and telogen hairs before chemotherapy and the extent of hair loss after chemotherapy. The hypothesis would be that patients with more telogen hairs are less prone to alopecia.

Before beginning treatment, the patient would be sent to the Dermatology Clinic for examination of his scalp hair roots. (See Crouse & Van Scott, 1960, p. 83, for details.) Photographs similar to those used in this study could be taken at the same time. Three months after treatments begin, photographs could again be taken. The photos could be compared and analyzed by the judges for extent of hair loss. Hair root examination would not need to be repeated as "no increase in numbers of resting hairs was observed following treatment with any of the drugs." (Crouse & Van Scott, 1960, p. 89)

The proposed study would not be experimental in design. Ideally,

patients with comparable disease receiving identical drugs should be studied. At the Portland Veterans Hospital, only the bronchogenic cancer patients on Protocol 16 could meet that criteria. In order to include a more diverse group of subjects in the study, a second group of patients with a variety of tumors who are all receiving notoriously epilating drugs could be studied as well. Other important variables to identify in this group would be age, type and extent of tumor, and nutritional status. Although the data from the first group would be more exact because dose relationships would not be a confounding variable, the addition of a second group would give more descriptive information about hair loss in cancers other than bronchogenic, and drugs other than Cyclophosphamide.

If there was indeed a positive correlation between telogen hairs and alopecia, and it was found that the hair of patients in the population stayed in telogen for longer periods of time than normal, it would simply remain to find a means of putting all the hairs of a cancer patient into telogen before beginning chemotherapy, to see whether this would prevent alopecia without adding new problems.

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APPENDICES

APPENDIX A

Consent Form

CONSENT FOR HUMAN RESEARCH PROJECT

I, _____ herewith
(First name) (Middle initial) (Last name)

agree to serve as a subject in the investigation named, The Effect of Scalp Tourniquet Use to Reduce Alopecia in Cancer Chemotherapy, under the supervision of Mary Maxwell, R.N. The research aims to determine whether scalp tourniquet use will reduce scalp hair loss in patients undergoing cancer chemotherapy.

I understand that my participation will involve:

1. Having five photographs of my head taken at the Veterans Administration Hospital before chemotherapy begins and each time that I come in for treatment for three months.

2. Having a scalp tourniquet inflated around my head each time I am receiving chemotherapy to prevent the blood containing the cancer drugs from reaching my hair follicles.

All information will be handled confidentially. My anonymity will be maintained on all documents, which will be identified by means of code numbers.

My participation does not involve any known risks. However, I understand that the scalp tourniquet may feel uncomfortable and my scalp will go to sleep.

I may not receive any direct benefit from participating in this project, but understand my contribution will help expand the knowledge regarding hair loss in people undergoing cancer chemotherapy. Hopefully, my hair may be spared by scalp tourniquet use.

I understand that I am free to withdraw from participation in

the investigation at any time without this decision otherwise affecting my medical treatment.

Mary Maxwell has offered to answer any questions I might have about the scalp tourniquet use in this study.

I have read the preceeding explanation and agree to participate as a patient in the study described.

Signature _____

Witness _____

Date _____

APPENDIX B

COCA Protocol

C O C A

PHASE I-II STUDY OF SEQUENTIAL (COCA) CHEMOTHERAPY IN SOLID TUMORS

Preliminary Protocol

1.0 BACKGROUND INFORMATION

1.1 In the active proliferative phase of cell growth, the individual cell undergoes four phases: (1) the so-called G 1 or gap 1, a resting phase between completion of cell division and beginning of DNA synthesis; (2) the S phase or the phase of DNA synthesis; (3) the G 2 or gap 2, a resting phase separating DNA synthesis from mitosis; and (4) the M or D phase or the phase of actual cell mitosis and cell division. There is also a non-proliferating pool in which the cellular cycle is abandoned and the individual cell is in a stage of differentiation and function, G_0. From the non-proliferating pool, cells may re-enter the proliferating pool under appropriate conditions; or, they may go on to the cell loss and death.

1.2 It is known in solid tumors that in the early stages of tumor growth, the exponential phase, many cells are in the proliferating pool. This has been shown by tritiated thymidine studies. There is a diffuse labeling throughout the tumor. As the tumor grows, a slowing phase is entered, and the volume doubling time increases. The volume doubling time of solid tumor malignancies is quite long:

many weeks to months. During this slowed phase, many cells enter the non-proliferating pool. Such cells are not vulnerable to agents which are cycle-specific.

1.3 It appears that most active antitumor compounds fall into two classes: (1) those that are cycle-specific which affect cells in active proliferation only, and (2) those that are cycle-nonspecific, which affect both the proliferating and non-proliferating cells.

1.4 In solid tumor chemotherapy, the use of single agents alone has at best yielded temporary palliation except in an occasional tumor type. Single agents used at maximal doses in sequence may take advantage of undue toxicity.

1.5 In addition to the determination of objective tumor response to this therapy, the modified criteria of Feinstein will be used to classify all patients. Feinstein has described the importance of staging the clinical extent of malignant disease to determine response to therapy.

2.0 PURPOSE OF THIS STUDY

2.1 The first purpose of this protocol is to study sequential chemotherapy to determine the true response rate of solid tumors to such treatment. The agents which have been selected are: (1) Cyclophosphamide, an alkylating agent which is not cycle dependent, to decrease the mass of tumor and result in a tumor of more actively cycling cells;

(2) Methotrexate, a cycle-specific, 3 phase agent; (3) Vincristine, the Periwinkle alkaloid specific for inhibition of mitosis; and (4) Actinomycin-D, Cosmagen, an antiibiotic which blocks RNA synthesis and which is probably not cycle-specific.

2.2 The second purpose of this study is to determine the value of clinical staging with regard to combination treatment.

3.0 METHODS

3.1 Patients

Patients will be eligible for study provided the diagnosis of incurable malignancy is determined as follows:

1. Histologic proof of the diagnosis of malignancy.
2. Local disease recurrent and no longer amenable to local surgery or radiation therapy, or disseminated cases.
3. Any previous chemotherapy within 8 weeks will make a patient ineligible for this study. Radiation therapy should be completed at least four weeks prior to consideration of treatment on this protocol.

3.2 Drug Administration

All patients who qualify for this study will be treated as follows:

1. Cyclophosphamide - 40 mgm/kg will be given in 100 ml 5% D_5W I.V. on day 1.
2. Vincristine - 2 mgm. directly I.V. will be given on Day 15.

3. Methotrexate - 0.6 mg/kg will be given directly I.V. on Day 29.
4. Actinomycin-D - 2 mgm will be given I.V. on Day 43.
5. After 14 days, or on Day 57, the sequence of drugs will be repeated with modification for hematologic toxicity:
   a.) WBC 4000 or greater and platelet count above 150,000 - give full doses.
   b.) WBC 3000-4000 or platelet count between 100,000 and 150,000 - give 1/2 dose.
   c.) WBC 2000-3000 or platelet count between 50,000 and 100,000 - give 1/4 dose.
   d.) WBC below 2000 or platelet count below 50,000 - no treatment.
6. Because Vincristine does not depress the bone marrow, full doses will be used despite reduced WBC and platelets.

3.3 Drug Toxicity

1. Cyclophosphamide - bone marrow depression (especially leukopenia), hemorrhagic cystitis.
2. Vincristine - peripheral neuropathy, constipation, alopecia.
3. Methotrexate - bone marrow depression, gastrointestinal toxicity, stomatitis, hepatitis, alopecia, skin rashes.
4. Actinomycin-D - bone marrow depression, gastrointestinal symptoms, stomatitis, skin rashes, alopecia.
5. Removal of patients from the study because of excessive

non-hematologic toxicity is preferable to omission or reduction of dosage because of the drug sequential nature of the study.

4.0 STUDIES BEFORE, DURING, AND AFTER TREATMENT

4.1 Baseline studies will include CBC with platelet count, routine urinalysis, blood chemistries (creatinine, alkaline phosphatase, and serum transaminase), and appropriate X-rays and radio-isotope studies.

4.2 Prior to each drug administration, the following studies will be done: CBC and appropriate blood chemistries. Careful observation for toxicities such as G.I. symptoms, peripheral neuropathy, etc. will be made. More frequent studies should be done if significant toxicity occurs.

4.3 Appropriate X-ray examinations will be repeated at least monthly.

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APPENDIX C

Karnofsky Activity Scale

KARNOFSKY PERFORMANCE STATUS SCALE

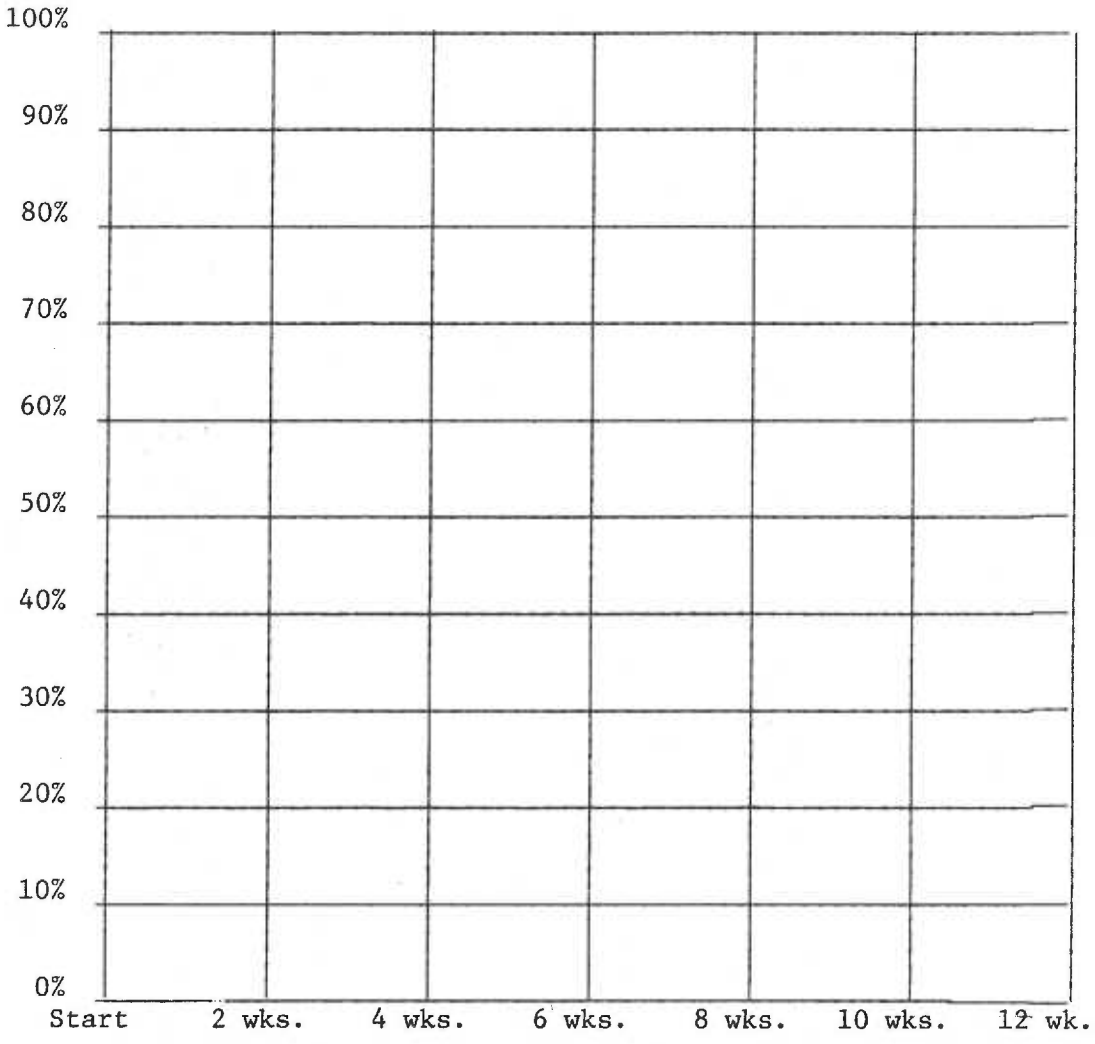
Able to carry on normal activity, no special care is needed.	100 Normal; no complaints, no evidence of disease
	90 Able to carry on normal activity; minor signs or symptoms of disease
	80 Normal activity with effort; some signs or symptoms of disease
Unable to work; able to live at home, care for most personal needs; a varying amount of assistance is needed.	70 Cares for self, unable to carry on normal activity or to do active work
	60 Requires occasional assistance but is able to care for most of his needs
	50 Requires considerable assistance and frequent medical care
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40 Disabled; requires special care and assistance
	30 Severely disabled; hospitalization is indicated, although death not imminent
	20 Very sick; hospitalization necessary, active supportive treatment is necessary
	10 Moribund, fatal processes progressing rapidly
	0 Dead

APPENDIX D

Form Used by Judges for Rating

Hair Loss, and

Instructions to the Judges


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Start
2 wks.
4 wks.
6 wks.
8 wks.
10 wks.
12 wk.

Instructions to the judges:

You are to inspect the pictures of each of these patients to determine hair loss over a period of time. The amount of hair exhibited on the first set of pictures will be considered 100% and will be the baseline for that patient. At each subsequent two-week interval, compare the pictures of each part of his head and determine what percent, if any, has been lost. (0 on the graph represents complete epilation.)

Please keep in mind that not all patients lose their hair during chemotherapy.

AN ABSTRACT OF THE CLINICAL INVESTIGATION OF

MARY BAHNER MAXWELL

For the MASTER OF NURSING

Date of Receiving this degree June 9, 1978

Title: THE EFFECT OF SCALP TOURNIQUET USE ON ALOPECIA IN CANCER CHEMOTHERAPY

APPROVED: _____
(Clinical Investigation Advisor)

The purpose of the study was to demonstrate the extent to which alopecia was slowed, reduced, or prevented by use of a scalp tourniquet to protect the hair follicles during cancer chemotherapy.

Nine patients with advanced bronchogenic carcinoma at a Veterans Hospital who were starting COCA chemotherapy were placed in experimental and control groups. A special inflatable scalp tourniquet was used on each patient in the experimental group during the time of peak plasma drug concentration at each treatment. Photographs of the head were taken at two week intervals for each patient for three months and were rated by judges at the termination of the study as to extent of hair loss.

There was no statistical difference in hair loss between the two groups, nor was hair loss slowed by the use of a scalp tourniquet. However, the data do reveal some differences in patterns of hair loss in these nine patients all receiving identical drugs. Two patients lost virtually all their hair, two lost almost none, and the rest fell somewhere in between.