

## Conference on Cancer of the Lip

### (Based on a Series of 3166 Cases)

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**C**ARCINOMA of the lip is recognized as the most common form of oral cancer. Though it is infrequent as a cause of mortality, patients with lip cancer constitute about 3% of all new cancer patients registered at the Ontario Cancer Foundation Clinics.

Who is the typical patient with cancer of the lip? From the mass of statistical data the following composite picture emerges of a male, 66 years of age, who is fair-skinned and probably works outdoors. He would have noticed a sore or blister on his lower lip but would delay seeking medical advice for six months. There is a one in 12 chance that he will develop metastatic nodes, but a 90% chance that his primary lesion will be readily controlled by radiotherapy.

At the 1962 Annual Conference of The Ontario Cancer Treatment and Research Foundation, held in Ottawa, the problem of cancer of the lip was reviewed in all its aspects. This communication is based on this Conference and quotes freely from the several presentations.

#### STATISTICAL DATA

The reader is referred to the article entitled "A Statistical Review of Carcinoma of the Lip" by Drs. E. N. MacKay and A. H. Sellers of Toronto, on page 670 of this issue. It reviews all of the material presented at the Conference and specifically deals with 3166 patients who had microscopically confirmed squamous cell carcinoma of the lip and who received part or all of their initial treatment at one of the Ontario Cancer Clinics. The manner in which the lip lesions were staged and the significant statistical data available on these patients are discussed, and occasional reference will be made in this communication to certain of the statistical data provided in the article of MacKay and Sellers.

#### PATHOLOGY

The detailed statistical review of carcinoma of the lip was purposely restricted to squamous cell carcinoma. All other types of invasive cancer were less than 3% of the total number under study. In common with the findings of others, it was the feeling of the participants that most cases of basal cell carcinoma were related to the cutaneous margin and were probably basal cell carcinoma of the skin.

DRS. M. O. KLOTZ and D. MAGNER of Ottawa reviewed representative groups of cases from the Ottawa Clinic (approximately 240 slides) in order to compare present-day methods of pathological evaluation with those in use at the time the slides were originally interpreted. In addition, in the course of this study an attempt was made to grade the degree of malignancy on the basis of Broders' staging (I-IV). Where a good specimen had been provided for examination, the pathologists were prepared to indicate the histological differentiation of the lesion as well-differentiated or poorly differentiated (anaplastic) tumour. It was felt that individual observer error and variation in interpretation would not permit any more definitive histopathological diagnosis.

Both Dr. Klotz and Dr. Magner concluded from the present study that 80-83% of patients classified in the Ottawa Clinic between 1946 and 1955 as having squamous cell carcinoma of the lip in fact had this disease. A further 5% did not have carcinoma in the light of modern knowledge and the criteria and classifications used (e.g. some had keratoacanthomas). The diagnosis in the remaining number of cases was considered equivocal and can be resolved only by time and further study.

The importance of the histological differentiation of the primary lesion is apparent when one compares the survival rate for a well-differentiated lesion, which has a net five-year survival rate of 93.6%, with that for an anaplastic lesion, namely, 64.5%. When metastatic nodes are present at the time of treatment of the primary lesion, patients with an anaplastic lesion have a five-year survival rate of only 28.6%; those with a differentiated lesion, 83.6%. DR. T. C. BROWN of Toronto in his review of the pathological presentation stated the situation well: "A simple classification of lip cancer into well differentiated and poorly differentiated bears a direct and significant relationship to the prevalence, the clinical course and the efficacy of treatment."

#### ETIOLOGY

DR. R. G. C. MACLAREN of Hamilton, in his consideration of the causes of carcinoma of the lip, pointed out that the same factors that affect the skin produce cancer of the lip. Thus, it is seen preponderantly in fair-skinned outdoor male workers who are affected by exposure of the lower lip to the sun, whereas the upper lip is partly protected. The difference in sex incidence, with a male-to-female ratio of 66:1, may be partially explained by the lessened exposure of women to sunlight and the partial protection to the lips offered by lipstick.

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Ultraviolet light will produce tumour growth quite readily in certain experimental animals, and the range of the carcinogenic wave length has been determined by many observers, with good agreement that it lies about 2900 A to 3300 A.

Calculation of the absorption gradient of ultraviolet light of about 3000 A shows that there is significant absorption in the dermis of fair-skinned individuals, whereas little passes the pigment of the basal layer in the dark skinned. Keratinization offers some protection, but this is not usually comparable to that of pigment.

Little is known of the mechanism whereby ultraviolet light produces neoplasia. Undoubtedly collagen degeneration in the tissues is related to the effect of ultraviolet light and is a feature in solar keratosis. No significant relationship has been established between smoking and cancer of the lip, in contrast to increased prevalence of cancer of the lung related to cigarette smoking.

Back through the years there have been a few cases reported of carcinoma of the lip developing, particularly in old people, after a previous herpes zoster or herpes simplex infection.

There are a number of predisposing factors to the development of cancer of the lip, and the earlier lesions produced by sunlight are readily recognized, such as chronic cheilitis or localized solar keratosis. Such other causes of chronic irritation as poorly fitting dentures, sharp teeth and poor oral hygiene all tend to complement the picture.

Dr. MacLaren summarized the picture as follows: "The lips represent a transitional zone between skin and mucous membrane of the mouth, are exposed to many types of irritation and are not infrequently involved by inflammatory processes without associated change in the skin or mucous membrane. In many cases the cause of the neoplastic change in the lip cannot be determined."

#### RELATIONSHIP OF SEX, AGE, SITE AND STAGE OF DISEASE

Squamous cell carcinoma of the lip is relatively infrequent in women, and the male-to-female ratio for all cases of squamous cell carcinoma in this series was 66:1. This ratio rose to 79:1 in relation to the lower lip, and fell to 18:1 in relation to the commissure and 10:1 in relation to the upper lip. Of the review group the upper lip was involved in 14.9% of the female cases and in only 2.5% of male cases. These figures tend to suggest that the etiological features responsible for the development of carcinoma of the lip in the male presumably are not operating to the same degree in women. Some authors feel that carcinoma of the lip is a sex-linked disease and this may explain the preponderance in the male.

In his review of these relationships to carcinoma of the lip, DR. J. FRAME of Kingston further stressed that the site of a carcinoma on the upper lip or

commissure, in contrast to the lower lip, is of particular importance, as the lymphatic drainage is more likely to permit metastatic dissemination not only to submandibular glands but to the cervical glands on either side. The increased incidence of lymph node involvement is reflected in slightly lower net survival rates for upper lip than lower lip and considerably lower rates for the commissural lesions.

The median age on admission was 64 years for men and 69 years for women in this series. The bulk of the cases occurred in the age group between 45 and 74 years. The net survival rate for the review group decreased with advancing age. Even when nodes were not involved on admission, a decrease in the net survival rate for each successive 10-year age group over 55 years was considered statistically significant and may have been related to a more advanced stage of the disease.

The overall net survival rates were similar for men and women, despite the differences in incidence in site of the lip lesions.

The actual size of the primary lesions was recorded in 15.7% of the group. It was noted that the metastatic node involvement increased and the net survival rate decreased with increase in size of the primary lesion. The changes were considered statistically significant only for lesions 3 cm. or more in diameter.

Extent of delay from the first symptom to treatment in this series was associated with a wide range of tumour sizes in each duration group, suggesting that all tumours do not grow at the same rate. The limited range of survival rates from one duration group to another suggests that early treatment is not the whole solution.

#### DIAGNOSIS

The initial first symptom in over half the cases was an ulcer, sore, blister or cold sore. About 8% had a crust, roughness or scab as the first symptom mentioned.

DR. ROBERT JACKSON of Ottawa in his dermatological review distinguished non-neoplastic lesions from those of carcinoma of the lip and stressed a number of important points. An actinic cheilitis with keratotic changes may clinically and pathologically resemble squamous cell carcinoma. Adequate biopsy and good clinical information are essential in such cases. Keratoacanthoma is difficult to distinguish in the early stages, and both the clinical and histological features must be considered in such a diagnosis. Other dermatological lesions such as lupus erythematosus and lichen planus have to be distinguished by their appearance and distribution elsewhere.

At this Conference it was further emphasized that small (1 cm.) submental or submaxillary glands have to be considered with respect, but they do not necessarily indicate the presence of metastatic involvement, and in many cases in this series

they disappeared after treatment of the primary lesion. Glands measuring 2 cm. or more, considered in relation to the site of the primary lesion, and distinguished by their firmness or fixation, usually indicate metastasis.

The most important feature in the entire diagnosis is an adequate biopsy and a clear and adequate history for the pathologist. Re-biopsy is always indicated if clinical suspicion remains high, and in some instances as many as three biopsies were necessary to verify the histological diagnosis.

#### TREATMENT

##### (a) *Radiotherapeutic Treatment of the Primary Lip Lesion*

Radiotherapy constituted the principal mode of treatment of the lip lesion in 92% of the review cases. The trend in the type of radiotherapy changed in the period under review. Whereas interstitial radium or radon constituted the favoured mode of treatment in the earlier years, this changed to external radiotherapy in the third six-year period to a point where 58% were treated by this means. Figures presented by Dr. MacKay and Dr. Sellers (see page 670 of this issue of the Journal) indicate that the initial radiotherapy treatment alone controlled the primary lesion in 85.3% of 2415 cases without node involvement traced five years or more.

The types of radiotherapy used showed some degree of variation from clinic to clinic and in relation to the site of the primary lesion.

In earlier years the majority of primary lesions of the lower lip were treated either by radium or radon-seed implantation. Reviewing radiotherapy treatment of carcinoma of the lip, Dr. W. E. C. ALLT of Toronto stated that the commissural lesions often have to be treated in the same manner as buccal lesions, and radium or cobalt needle interstitial implantation may be valuable. In one centre radioactive tantalum wire is used interchangeably in treatment of these commissural lesions.

Several Foundation clinics continue to use radioactive gold grains interstitially (superseding previous radon seeds) in treatment of small localized lesions of the lower or upper lip. The immediate advantage of this mode of treatment is that it can be done on an outpatient basis in one sitting under local anesthesia. This method is therefore useful in the treatment of a small lesion in an elderly outpatient or in a patient living remote from the treatment centre.

The statistical review tends to suggest that later metastatic node involvement may occur more readily after interstitial radiation than after external radiotherapy. This finding could be related to the site of the primary lesion rather than to the method of treatment.

As mentioned previously, the overwhelming trend is toward external radiotherapy. The statistical figures show that most of this external radiotherapy was given by x-ray at a kilovoltage below 200 kv.

Dr. Allt in his review of this aspect of treatment recommended (with the exception of a very superficial lesion) roentgen therapy in the range of 200-250 kv., H.V.L. from 0.2-0.5 mm. copper, with a given dosage of 4000-4500 rads (corrected for field size) in 10 treatments over two weeks. Use of a protective lead shield behind the lip and a second to expose about 1 cm. of normal tissue about the primary lesion is invariably recommended. In interstitial implants utilizing radium or tantalum wire Dr. Allt recommended a dosage of 6500 rads in five to five and a half days.

##### (b) *Surgical Treatment of Primary Carcinoma of Lip*

Application of surgery to primary carcinoma of the lip depends usually to some degree on the philosophy of the physician or surgeon and surgery was rarely used in the review series. It was agreed that surgery is the treatment of choice in those cases which have shown recurrence following local radiotherapy and in patients in whom there has been damage with some subsequent necrosis.

Extensive involvement of the lip extending into the adjacent soft tissues and even into bone may require radical surgical extirpation as the only means of providing a curative treatment.

Those patients with a chronic cheilitis, or carcinoma *in situ* present in the vermilion border, lend themselves to the procedure of a so-called "lip shave", described by DR. L. J. MAHONEY of Toronto.

##### (c) *Surgical Treatment of Regional Lymph Node Metastasis*

In common with other types of oral carcinoma, the treatment of metastatic lymph nodes is preferably surgical. DR. D. W. MACKENZIE of London felt that before such an undertaking is carried out, the following surgical requirements should be fulfilled: (a) The general condition of the patient should be good in respect of the expectancy of life and other disease conditions. (b) The primary lip lesion should be under control. (c) Local operability—the metastatic nodes must be locally removable. If one must cut through malignant tissue in order to perform the operation chosen, the procedure is best not performed. Furthermore, bilateral metastatic nodes do not constitute a contraindication to radical neck dissection.

Dr. MacKenzie classified the surgical procedures available for removal of metastatic nodes as follows: (1) local excision, (2) modified dissection, (3) radical neck dissection, (4) bilateral radical neck dissection, and (5) radical discontinuity procedures.

There is surgical agreement that in order to remove all the metastatic nodes and adhere to the principles of good cancer surgery a radical dissection must be performed. SIR STANFORD CADE of London, England, stressed that strict criteria of

operability must be observed and only mobile non-adherent lymph nodes should be submitted to block dissection. Dissection should start at the level of the mandible and extend to the level of the clavicle. It should include the deep fascia from the mid-line anteriorly to the anterior border of the trapezius muscle. Internal jugular vein, sternomastoid and digastric muscles should be removed. It was further pointed out that partial dissection of the neck was always a compromise and hardly ever successful.

Incontinuity procedures were considered to be reserved for those instances where the local lesion had involved bone, necessitating removal of part of the mandible.

Prophylactic neck dissection was not recommended, and a review of the statistical figures in this series suggested that perhaps only about one out of 14 patients would be helped by prophylactic dissection. The corollary to this statement is that regular and close follow-up of these patients is a necessity. Involved nodes present on admission were controlled by surgery in 47% of the 62 patients so treated (see Table III of paper by MacKay and Sellers), and nodes that became involved after initial treatment of the primary lesion were controlled by surgery in 50% of the 108 cases so treated. The real significance of the presence of involved lymph nodes, however, is noted in the finding that there was only a 58% five-year net survival rate for those who had metastatic node involvement when first seen.

#### (d) *Radiotherapy in Treatment of Metastatic Lymph Nodes*

This aspect of the treatment of involved nodes from carcinoma of the lip was carefully examined by Dr. D. H. THOMSON of London. Radiation has long been recognized for its importance in controlling or restraining the growth of neoplastic cervical lymph nodes. The patients are usually in a quite different category from the surgical candidates. Although primary surgical treatment of the metastatic lymph nodes is preferred, it is unfortunately the case that not all patients with cervical lymph nodes are operable, either because of local extent, the general condition of the patient or the uncontrolled nature of the primary tumour. In addition, preoperative radiation is recommended for the anaplastic carcinoma involving lymph nodes.

It is considered that cobalt-60 radiation is indicated for preoperative, postoperative and primary situations, and the interstitial use of gold grain or needle implants now tends to be supplementary to external radiation in specific instances.

Dr. Thomson pointed out that preoperative radiation may be used when regional lymph nodes are involved and operable; the purpose of radiation is to act as a holding procedure during treatment of the primary lesion. This does not interfere with subsequent performance of block dissection, which

is usually deferred until the primary tumour is controlled. It is possible that some safety against local spread at the time of surgery is achieved by preoperative radiation. It should be said, however, that the truly inoperable mass never becomes operable and the decision regarding surgery must be made prior to radiotherapy.

Postoperative radiation is recommended only if residual disease is considered to be present.

Primary radiation may be used for technically inoperable fixed metastatic nodes either as a palliative measure in the aged or with uncontrolled primary disease. It may be the only curative measure available when the primary lesion is controlled and the patient is in good condition.

The technical means of administering this cobalt therapy may be by a single direct field, particularly for palliation or in the preoperative group. A more radical approach would require parallel opposing or wedge fields, plus the use of bolus, to improve the homogeneity. It is considered that a dosage of 6000-6500 rads in four to five weeks is necessary to eradicate the primary squamous cell carcinoma, and secondary metastatic node involvement will require a similar dosage. Preoperative radiation consisted of a dosage of 3000-4000 rads in two to three weeks. Postoperative radiotherapy usually aimed at a dosage of 5000-6000 rads in five to six weeks, depending on the field size and the residual disease present. A further suggestion was made that preoperative radiotherapy to the gland-bearing areas in conjunction with subsequent surgery might be a subject for future control series, especially where an anaplastic type of primary carcinoma was demonstrable.

#### CONCLUSIONS

It is possible to draw the following conclusions from the presentations at this Conference based on a study of over 4000 cases of carcinoma of the lip of which 3166 were microscopically confirmed squamous cell carcinomas. (1) Primary carcinoma confined to the lip can be controlled satisfactorily by appropriately administered radiotherapy in approximately 85% of cases. (2) Metastatic node involvement is best dealt with surgically. The presence of nodes reduced the five-year net survival rate to 58%. (3) Prophylactic neck dissection is not recommended. From the statistical figures in this series it has been estimated that perhaps only one out of 14 patients would be helped by this prophylactic surgical procedure. (4) External cobalt-60 radiotherapy was the recommended treatment of inoperable metastatic node involvement. (5) The prognosis is much poorer for lesions at the commissure and somewhat poorer for those involving the upper lip than for lower lip lesions. Distribution by site differs for the two sexes. (6) Age of the patient and histological grading as well as size and site of the lesion influence net survival rate. (7) The findings in this review support the

tentative TNM system of staging for lip cancer as providing excellent prognostic criteria. (8) Over three successive six-year periods the pattern of radiotherapeutic treatment of the primary lip lesion changed in favour of external x-ray therapy. There was an improvement in the net survival rate over the period 1938-1955. (9) Excessive solar exposure of the lower lip seems to be a contributing cause of carcinoma of the lip. The use of a simple ointment or protective lipstick by outdoor workers should be considered.

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## A Statistical Review of Carcinoma of the Lip

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**I**N ONTARIO at present only about 13 men and one woman die each year from cancer of the lip, but this disease contributes 3% of all new cases registered at the Ontario Cancer Clinics, or some 250 new cases annually.

### SURVEY MATERIAL

In the years 1938 to 1955 inclusive, 4069 patients with clinically diagnosed lip cancer were registered at the eight Ontario Cancer Clinics. Of these, 3166 patients had microscopically confirmed squamous cell carcinoma of the lip and received part or all of their initial treatment at the Clinics. These 3166 patients constitute the "review group".

The upper lip was involved in only 3% of male cases, but in 28% of female cases. Both lips or the commissure were initially involved in 1 to 2% of cases. Lymph node involvement on admission was similar (8 to 9%) for upper lip and lower lip lesions, and higher (19%) for commissural lesions. Lymph node involvement during the course of disease was also higher for the commissural lesions. These differences were reflected in the survival rates.

Of all cases registered, 82% were histologically confirmed as squamous cell carcinoma. Basal cell carcinoma was diagnosed in only 36 cases or 0.9% of all cases registered.

This article was prepared at the request of The Ontario Cancer Treatment and Research Foundation for a Clinical Conference on Carcinoma of the Lip held at The Ontario Cancer Foundation's Ottawa Clinic, October 26, 1962; and based on data routinely recorded on the follow-up cards, maintained by the Foundation's Clinics.

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### ABSTRACT

Among 3166 patients with microscopically confirmed squamous cell carcinoma of the lip registered at The Ontario Cancer Treatment and Research Foundation's Regional Clinics in 1938-1955, the five-year crude survival rate was 65%, and the five-year net survival rate 89%. Survival was influenced by age, site and size of primary lesion, local and regional invasion, long delay, and treatment method. The initial treatment appeared to control the primary lesion in 84% of cases and involved lymph nodes in 58%. The net survival rates improved over the survey period. Findings confirm the usefulness of the proposed TNM staging.

Histological grading was recorded for only 461 cases. When the 649 lesions in grade 1 or 2 or "well differentiated" were contrasted with the 37 lesions in grade 3 or "poorly differentiated", the former group tended to have smaller lesions although the pretreatment durations were comparable. The differentiated lesions were also associated with higher survival rates, and 86% were apparently controlled by the initial treatment as compared with only 62% of the anaplastic lesions.

The male-to-female ratio for the whole survey period was 50:1. It ranged from two males to one female for basal cell carcinoma and 5:1 for upper lip lesions to 79 males to one female for squamous cell carcinoma of the lower lip. For the years 1950-