CANCER OF THE TONGUE, MOUTH, AND PHARYNX

SEX DIFFERENCES IN PROGNOSIS FOLLOWING RADIOTHERAPY*

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In the presentation of morbidity and mortality surveys of malignant disease in sites affecting both sexes it is customary for the sex incidence rates to be stated separately. This principle is rarely observed, however, in the presentation of treatment results. Omission of the sex factor, in a series of cases large enough to render separate analyses practicable, may well have the effect of concealing real differences in prognosis. The object of this survey is to demonstrate, by separate sex analysis of the comparative results of treatment of cancer of the tongue, mouth, and pharynx, that such results not only can exist but may be substantial.

It is shown that in females the overall treatment results are much higher, and that post-operative mortality, recurrence rate, and incidence of secondary lymph nodes are lower.

Basis of the Survey.—The data analysed are from 673 cases of cancer of the tongue treated by radium implantation, 916 cases of cancer of the mouth, and 550 cases of cancer of the pharynx—a total of 2,139 cases treated by radium or deep x rays at the Christie Hospital and Holt Radium Institute, Manchester, during the years 1932 to 1942 inclusive. Evaluation of differences in response has been conducted in relation to the state of affairs ten years after treatment.

Criteria of Classification

The primary sites conform to International List Nos. 141-6, with the exception of soft palate, which is excluded from the sites covered by No. 144, and fauces and tonsil, which are excluded from No. 145, for reasons which are explained later.

For the purpose of presenting the findings in concise form, subdivisions in tables have been kept to a minimum, although the data have actually been analysed first in greater detail to ensure that no bias would be introduced by this procedure.

Although this survey is not concerned with the evaluation of particular treatment methods, it is necessary to state—again in the interests of eliminating possible bias—that no sex discrimination was exercised in the application of particular techniques. For tongue cases radium implantation was used; for mouth and pharynx the techniques employed were (a) radium used by intracavitary, interstitial, or surface applicator method; (b) deep x-ray therapy. Where technically and physically practicable, cervical lymph node involvement was dealt with by block dissection: in a proportion of cases no form of treatment was deemed useful; in others, radiation was used as an alternative. No significant difference was found between the sexes in the proportions of the various techniques or between the four clinical stages of advancement.

The term "node-free" implies that in the cases so described there was no clinical evidence of cervical lymph node involvement at the time of treatment; the group

represents summation of stages I and II according to the convention devised at the Christie Hospital and Holt Radium Institute, and, since its adoption elsewhere, known as the Manchester staging. Full details of the staging convention were given by Paterson, Tod, and Russell (1950). The term "nodes involved" indicates the presence of clinically palpable lymph nodes at the time of treatment, and represents summation of stages III and IV. Distant metastases rarely occurred, and almost invariably there already was cervical invasion. No useful purpose seemed to be served, therefore, by reporting them in this particular study.

Statistical Method

In the tables relating to 10-year survival the description "age-corrected rate" means that the crude rate has been corrected by age as a factor in the assessment of treatment results, this rate having been calculated by application to the crude survival rate of a weighted probability designed to correct for deaths due to intercurrent causes with no evidence of residual or recurrent cancer at the time of death. If any realistic picture of 10-year results is to be obtained such a correction is essential. The crude survival rate is included for purposes of comparison, although it under-evaluates the long-term effect of cancer treatment. A detailed account of the age factor method of correction was discussed and applied by Paterson *et al.*

Percentages are shown rounded off to the nearest whole digit. Statistical tests of significance have been applied to the results, and in commenting on the differences the following convention is adopted: the term "significant" is in general used when the observed differences exceed the conventional level of twice the standard deviation to a limit of 2.57. The probability of the difference in results being due to chance would thus range from 1 in 20 to 1 in 100. Where the differences meet even more stringent tests they are referred to as "highly significant." In some instances, where the distributions indicate the desirability of a different statistical method of evaluation, the same criterion of significance obtains.

Section I. Cancer of the Tongue and Mouth

Sex Differences in Distribution and Response

Table I gives the distribution in terms of sex incidence and primary site of the data for analysis. The sex ratio male to female on the total cases in tongue and buccal cavity respectively is almost identical, but there are marked

TABLE I.—Data for Investigation

Primary Site	Cases	Males	Females	Ratio Males to 1 Female
Tongue:				
Anterior two-thirds ..	522	422	100	4.2
Posterior one-third ..	151	138	13	10.6
Total ..	673	560	113	5.0
Buccal cavity:				
Floor	427	395	32	12.3
Cheek	215	160	55	2.9
Lower alveolus/gum ..	177	144	33	4.4
Upper	34	20	14	1.4
Hard palate	63	49	14	3.5
Total ..	916	768	148	5.2

differences between individual sites. It is noticeable, for example, that comparatively few women have lesions arising in the posterior third of the tongue. It is equally noticeable from the distribution of the anterior buccal cavity cases that, in men, lesions arising in the lower part of the mouth predominate, although this is not so in women. The word "incidence" in this context is, of course, used in the restricted sense of describing the relative frequency of the treated cases for investigation. Incidence rates and their changing pattern, based on a defined population, are the subject of a separate survey in course of preparation.

*This paper, confined to cancer of the tongue, was read at the 7th International Congress of Radiology held in Copenhagen, July 19-25, 1953. Mouth and pharynx cases have since been investigated on similar lines, and the results are now embodied in the paper.

Reference has already been made to the exclusion of the soft palate. Technically and aetiologically this site seems to be more suitably grouped with the posterior buccal cavity (or faucial) region. During the years under review 656 cases arising in fauces, tonsil, and soft palate were treated, distributed as follows:

	Males	Females	Ratio Males to 1 Female
Fauces ..	368	15	24.5
Soft palate ..	161	2	80.5
Tonsil ..	100	10	10.0
	629	27	23.3

These figures indicate the futility of investigating sex differences in prognosis in this particular region. When the hard-palate and soft-palate cases are grouped together—in the present instance giving a sex ratio male to female of 13.1:1—the great disparity in the ratios for hard and soft palate separately (3.5:1 and 80.5:1) is obscured.

This characteristic of very low incidence in women is, as is well known, also common to the lip—a site which is sometimes included in mouth surveys, but which again is rendered impracticable in this context by the paucity of female cases.

The age distribution by sex, expressed as a percentage, is shown in quinary groups in Fig. 1. In women the disease manifests itself at an earlier age than is the case in men. Thus, in the tongue cases the modal age group occurs a decade earlier, and in the mouth cases five years earlier. Reference is made later to the need for taking into account these disparities in age distribution.

In Table II the 10-year results for the two groups of cases are shown separately by sex. Crude survival and age-corrected rates reveal considerable differences between males and females. Although, as previously stated, age-corrected rates offer a better assessment of the efficacy of treatment, the differences between the crude survival rates are of much the same order and are highly significant.

If the overall survival rate is considered in relation to cervical lymph node involvement at the time of treatment

of the primary lesion (Table III), the analysis is seen to yield the same trend of a higher rate in women, although, not unexpectedly, the differences in the later stages of the disease are not statistically significant. In the node-free group, however, the differences are highly significant.

It is pertinent to examine next the various factors contributing to the overall differences already demonstrated. The factors for investigation are: post-operative mortality; incidence of recurrence; incidence of cervical lymph nodes before treatment; subsequent cervical involvement.

Post-operative mortality is the first major hazard to be encountered after treatment. It is logical to deal with it first from a statistical point of view also, since its impact somewhat reduces the number of cases available for in-

FIG. 1.—Age distribution of cases of cancer of the tongue and buccal cavity given radiotherapy during 1932-42.

vestigation of other phenomena. Table IV shows that, whereas the post-operative mortality rate for men with cancer of the tongue is 15%, the corresponding rate for women is only 4%—a difference which is highly significant. In the buccal cavity, where there is an apparently lower risk

TABLE II.—Comparison by Sex of 10-Year Survival Rates

Sex	Tongue			Buccal Cavity		
	No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Male	560	13%	23%	768	18%	32%
Female	113	31%	42%	148	34%	47%
Total	673	16%	26%	916	20%	32%

(a) $P < 0.0001$. (b) $P < 0.0001$.

TABLE III.—Comparison by Sex and Clinical Findings of 10-Year Survival Rates

Clinical Findings	Sex	Tongue			Buccal Cavity		
		No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Node-free	M	352	20%	35%	416	25%	46%
	F	85	38%	51%	91	46%	71%
Nodes involved	M	208	2%	4%	352	9%	16%
	F	28	11%	13%	57	12%	18%

(a) $0.0001 < P < 0.001$. (b) $P < 0.0001$. (c) $P = 0.08$. (d) $P = 0.40$.

TABLE IV.—Comparison by Sex and Age of Post-operative Mortality

Age Group	Tongue				Buccal Cavity			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Under 50	38	0%	20	0%	44	7%	23	0%
50-59	124	17%	37	0%	159	7%	44	5%
60-69	273	16%	36	8%	347	6%	52	6%
70+	125	17%	20	10%	218	10%	29	3%
Total	560	15%(a)	113	4%(a)	768	7%(b)	148	4%(b)

(a) $0.001 < P < 0.01$. (b) $P = 0.20$.

to men, the difference between male and female rates of 7% and 4% does not reach the conventional level of statistical significance, the probability of chance occurrence being 1 in 5. The fact that there is a heavier weighting of men in the higher age groups has already been shown. Nevertheless, the analyses in both tongue and buccal cavity groups reveal a male excess mortality in most age groups.

Having observed striking sex differences in the post-operative mortality rate, it is worth while to look at these

further in relation to the effects of lymph node involvement. The figures for node-free tongue cases show (Table V) a significant difference in the rates of 10% and 2%. Node-free mouth cases provide the only instance of an equal rate for men and women. This is apparently due to the combined effect of known cardiac disease and old age in two

TABLE V.—Comparison by Sex and Clinical Findings of Post-operative Mortality

Clinical Findings	Tongue				Buccal Cavity			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Node-free	352	10%(a)	85	2%(a)	416	4%	91	4%
Nodes involved ..	208	25%(b)	28	11%(b)	352	11%(c)	57	4%(c)

(a) $0.04 < P < 0.05$. (b) $P = 0.15$. (c) $P = 0.12$.

of the four deceased women in this group. Where lymphatic spread had occurred, appreciable differences exist between men and women in the respective rates of 25% and 11% for tongue and 11% and 4% for mouth, although they do not reach the significant level owing to the fact that the female groups are comparatively small. It should be borne in mind, of course, that these mortality rates were experienced in the years before antibiotics were in general use. Substantial reductions in post-operative mortality have been achieved since their introduction. Despite this beneficial effect, it is interesting to observe that an advantage still lies with females.

The next comparison to be made is the important one of recurrence rate of the primary lesion. This is evaluated more clearly by confining analysis to cases originally classified node-free. The term "recurrence rate" is a convenient one to use, but it has a wider application in this context than it has when used in relation to radical surgery. As the post-treatment phase for tumours treated *in situ* is one of regression at varying rates, apparent quiescence of a residual lesion or—in tumours of a completely radio-resistant character—steady advancement of the malignant process, recurrence rate actually implies apparent failure of the primary to resolve completely as well as recurrence after an interval of freedom from sign or symptom.

It has been necessary to deduct the post-operative deaths from this group, since these cases were no longer available for observation. In Table VI, which for tongue cases shows

TABLE VI.—Comparison by Sex of Incidence of Primary Recurrence in Node-free Group (After Deduction of 98 Post-operative Mortality Cases)

Sex	Tongue		Buccal Cavity	
	No. Observed	Primary Recurrence Rate	No. Observed	Primary Recurrence Rate
Male	318	41% } (a)	360	36% } (b)
Female	83	21% }	85	22% }

(a) $0.0001 < P < 0.001$. (b) $0.01 < P < 0.02$.

TABLE VII.—Comparison by Sex of Incidence of Cervical Lymph Nodes Before Treatment

Clinical Findings	Tongue		Buccal Cavity	
	Males	Females	Males	Females
Node-free	352	85	416	91
Nodes involved ..	208	28	352	57
Total ..	560	113	768	148
Proportion with nodes involved	37% 25% (a)		46% 39% (b)	

(a) $0.01 < P < 0.02$. (b) $P = 0.10$.

a primary recurrence rate of 41% in men as opposed to 21% in women, a highly significant difference is demonstrated. The rates of 36% and 22% for mouth cases similarly disclose that recurrence is much less frequent in women than in men, the observed difference being significant.

Sex differences in cervical lymph node involvement at the time of original examination are shown in Table VII. In both tongue and mouth lesions a higher rate exists in males than in females: in the former group the difference is near to high significance; in the latter it is not significant at the conventional level, the probability of chance occurrence being 1 in 10. Nevertheless, these trends suggest the desirability of investigating the incidence of lymph nodes after treatment of the primary lesion in the group of cases originally classified as node-free.

The results of the analysis of the final factor investigated are shown in Table VIII. For tongue lesions the greater susceptibility of men to subsequent cervical involvement is

TABLE VIII.—Comparison by Sex of Development of Cervical Lymph Nodes in Cases Originally Node-free (After Deduction of 98 Post-operative Mortality Cases)

Sex	Tongue		Buccal Cavity	
	No. Observed	Lymph Node Incidence Rate	No. Observed	Lymph Node Incidence Rate
Male	318	60% } (a)	360	49% } (b)
Female	83	47% }	85	27% }

(a) $P \approx 0.03$. (b) $0.0001 < P < 0.001$.

indicated by the male and female rates of 60% and 47% respectively, and is statistically significant. The same trend is disclosed in the mouth group, in which the difference between the rates of 49% and 27% is highly significant.

Section II. Cancer of the Pharynx

Difficulties implicit in dealing with cancer in this site are inevitably encountered in attempting to investigate sex differences in prognosis according to the pattern adopted in Section I. In a site of such unfavourable prognosis clinical and technical handicaps are unavoidably reflected in any statistical evaluation, and consequently less precision is attainable in the assessment of certain characteristics. The same trends of better prognosis in the female are nevertheless demonstrable, and seem to be worth recording in somewhat condensed form.

TABLE IX.—Data for Investigation

Primary Site	Cases	Males	Females	Ratio Males to 1 Female
Nasopharynx and oropharynx	287	208	79	2.6
Hypopharynx and post-cricoid	263	141	122	1.2
Total	550	349	201	1.7

Sex Differences in Distribution and Response

The data for analysis are divided into two broad groups, as shown in Table IX. In the nasopharynx and oropharynx the frequency ratio indicates much less disparity between the sexes than is the case for the tongue and mouth, and scarcely any for lesions arising in the hypopharynx and post-cricoid region.

Figure 2, giving the age/sex distributions, shows no difference in the modal age group for males and females in the nasopharynx and oropharynx. As there were more patients in the younger age groups than was the case in tongue and mouth lesions, the range of quinary age groups has been expanded. The distribution for hypopharynx and post-cricoid region shows a sharp rise to the modal age of 65-69 for males, the corresponding peak for females being 60-64.

FIG. 2.—Age distribution of cases of cancer of the pharynx given radiotherapy during 1932-42.

Comparison by Sex of 10-Year Survival Rates

A highly significant difference between males and females is shown for the nasopharynx and oropharynx group (Table X). It may also be observed that the 10-year results for women are as good as the survival rates experienced by men with cancer of the tongue. On the other hand, the long-term results for hypopharynx and post-cricoid region cases reveal uniformly poor prognosis.

TABLE X.—Comparison by Sex of 10-Year Survival Rates

Sex	Naso- and Oropharynx			Hypopharynx and Post-cricoid		
	No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Male ..	208	6%	8%	141	3%	5%
Female ..	79	19%	23%	122	2%	3%
Total ..	287	9%	12%	263	3%	4%

(a) $0.0001 < P < 0.001$.

TABLE XI.—Comparison by Sex and Clinical Findings of 10-Year Survival Rates

Clinical Findings	Sex	Naso- and Oropharynx			Hypopharynx and Post-cricoid		
		No. Treated	Crude	Age-corrected	No. Treated	Crude	Age-corrected
Node-free	M	28	7%	12%	39	5%	9%
	F	19	16%	21%	48	4%	6%
Nodes involved	M	180	6%	7%	102	2%	4%
	F	60	20%	24%	74	1%	2%

(a) $P = 0.65$. (b) $0.0001 < P < 0.001$.

TABLE XII.—Comparison by Sex and Age of Post-operative Mortality

Age Group	Naso- and Oropharynx				Hypopharynx and Post-cricoid			
	Males		Females		Males		Females	
	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate	No. Treated	P.O. Rate
Under 50	44	9%	27	0%	8	13%	26	12%
50-59 ..	41	5%	21	5%	21	38%	41	17%
60-69 ..	90	23%	26	12%	76	21%	48	13%
70+ ..	33	15%	5	0%	36	17%	7	14%
Total ..	208	15%(a)	79	5%(a)	141	22%(b)	122	14%(b)

(a) $0.02 < P < 0.05$. (b) $P = 0.09$.

Analysis according to the presence or absence of cervical lymph node involvement (Table XI) is not very profitable in view of the low numbers in the node-free group of nasopharynx and oropharynx cases and the poor results already seen in Table X for hypopharynx and post-cricoid region cases. Nevertheless, the trend in the former again shows an appreciably higher rate for women, which might well prove to be a significant one if more cases were available for study. Where cervical involvement had taken place the higher survival rate for women is highly significant.

Table XII reveals the overall post-operative mortality rates for cancer of the nasopharynx and oropharynx to be almost identical with those for cancer of the tongue, and significantly higher in males. Unlike the tongue and mouth cases, however, the heaviest rate for each sex occurred in the decade 60-69. The difference of 8% between the male and female rates for hypopharynx and post-cricoid, although not great enough to be statistically significant, follows the same trend.

Analysis of the cases according to cervical lymph node involvement also shows a similar trend throughout of a higher rate for men, but the consequent decrease in numbers in each group results in none of the differences being significant. No useful purpose seemed to be served, therefore, by the inclusion of a table in this form.

It is not practicable in this section to include a table dealing with recurrence of the primary lesion in node-free cases, as was done in Section I. Complications such as oedema and stenosis encountered in the hypopharynx and post-cricoid region result in any attempt at assessment being highly presumptive, even with an endoscopic examination and biopsy, and consequently undesirable as a basis of statistical evaluation. In the nasopharynx and oropharynx the same difficulties exist, but in a lesser degree. It seems probable here that 57% of men and 42% of women experienced recurrence in the primary site, but this assessment must be regarded as being less reliable than that quoted for the tongue and the mouth.

TABLE XIII.—Comparison by Sex of Incidence of Cervical Lymph Nodes Before Treatment

Clinical Findings	Naso- and Oropharynx		Hypopharynx and Post-cricoid	
	Males	Females	Males	Females
Node-free ..	28	19	39	48
Nodes involved ..	180	60	102	74
Total ..	208	79	141	122
Proportion with nodes involved ..	87%		72%	
	(a)		(b)	

(a) $P = 0.03$. (b) $0.04 < P < 0.05$.

Cervical lymph node involvement prior to treatment of the primary lesion, which is the subject of analysis in Table XIII, occurs in both sexes to a far greater extent when the primary is situated in the pharynx than is the case when it is in the tongue or mouth. In each pharyngeal subgroup the rate for males is shown to be significantly higher than that for females.

Assessment of the risk of cervical lymph node involvement developing after treatment of the primary lesion is, of course, influenced by the response to treatment of the latter.

Where the prognosis is poor, the opportunity for observation of various characteristics is correspondingly limited. Furthermore, the node-free groups are small (Table XIII). It suffices to say, therefore, that the respective rates of 22% for males and 16% for females in nasopharynx and oropharynx cases, and 24% for males and 13% for females in hypopharynx and post-cricoid cases, follow the same trend as was observed for cervical invasion before treatment. The fact that these rates are so much lower than the comparable ones shown for the tongue and mouth cases is attributable to the shorter average duration of life. In the event of any future development of more effective methods of controlling the primary lesion they could not be regarded as an authentic estimate of potential lymph node involvement.

Discussion

Summarizing the findings, then, it would seem that in the treatment of cancer of the tongue, mouth, and pharynx female patients may be expected to respond much better than males and to resist lymphatic spread more successfully. In none of the aspects investigated—namely, long-term survival, incidence of post-operative mortality, primary recurrence, secondary lymph nodes before and after treatment of the primary lesion—has any evidence against this thesis emerged.

The fact that such sex differences in prognosis are demonstrable makes it obvious that, in the presentation of the results of treatment, omission of the sex and age distribution may well affect the deductions to be made from survival rates. Failure to keep this in mind may conceivably be the cause of some misinterpretation, since, in making comparisons, a higher survival rate attributed to improved technique may be due merely to differences in the sex ratio in the sample.

Furthermore, the need for the incorporation of an age-factor correction cannot be too strongly emphasized, particularly in countries where there is a rapidly increasing proportion of old people in the population. The consequent rising proportion of deaths from intercurrent diseases invalidates the crude mortality rate for purposes of treatment evaluation.

Revelation of differences in behaviour inevitably arouses speculation regarding the causes. Three obvious lines of inquiry seemed to be: (a) the possible effect of oestrogen changes; (b) the comparative incidence of syphilis; and (c) the respective standards of oral hygiene. Analysis of the results on a pre- and post-menopausal basis failed to reveal any real difference. The cases in which a Wassermann test had been made were invalidated for statistical purposes by the policy of clinical selection. Investigation of dental sepsis could not be undertaken in a survey of retrospective character, but there is a strong suggestion from various sources that the standard of oral hygiene is appreciably higher in women than in men.

It may be that investigation of possible local influences would yield only a partial solution, and that the differences now demonstrated are merely a cogent example of the fact that the female, although lacking equal physical strength, is nevertheless fundamentally possessed of greater stamina than the male. In a comparison of male and female mortality trends, Martin (1951) showed that the disadvantage experienced by males has been increasingly enhanced during the past few decades. An analogy is to be found in various other species in which there is an excess mortality of males over females.

Despite the fascination of speculation, the initial function of the statistician is to indicate where such sex differences in prognosis exist, in the hope that medical research workers from other fields may be induced to explore some of the by-ways.

Summary

Three groups of cancer cases—673 in the tongue, 916 in the buccal cavity, and 550 in the pharynx—treated by radium or deep x rays at the Christie Hospital and

Holt Radium Institute, Manchester, during the years 1932 to 1942 inclusive are analysed separately by sex ten years after treatment, for the purpose of demonstrating a marked difference in prognosis.

Survival rates are given in terms of the whole group irrespective of the degree of clinical involvement at the time of treatment, and also in relation to the presence or absence of extension of the disease to cervical lymph nodes. Relevant factors, including post-operative mortality, incidence of recurrence, and incidence of cervical lymph nodes before and after treatment of the primary lesions are investigated.

In all the directions explored the same trend emerges in support of the thesis that a much better response to treatment is manifest in women than in men. Women are also less prone to develop metastases. Some possible influences are considered.

The opinion is expressed, that, in the presentation of the results of treatment of malignant disease, failure to state the sex and age distribution may result in fallacious deductions when comparisons are being made between different series of cases. Attention is also directed to the inadequacy of the crude survival rate for purposes of long-term evaluation, and the necessity for incorporating an age-factor correction is emphasized.

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CANCER OF UTERUS: RELATIVE INCIDENCE OF TYPES

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Carcinomas of the uterus are commonly divided into three groups: (1) epidermoid carcinoma of the cervix; (2) adenocarcinoma of the cervix; and (3) endometrial carcinoma of the "body." The first and third groups together account for over 90% of uterine carcinomas.

Cases under Review

During the past four years 1,612 uterine specimens have been examined in this hospital. These were composed of endometrial curettings, 1,135; uteri, 286; and cervical biopsies, 191. During this period carcinoma of the body has been diagnosed in 34 cases, epidermoid carcinoma of the cervix in five cases, and adenocarcinoma of the cervix in one case.

The age distribution of the cases of adenocarcinoma of the endometrium is shown in the Table. The mean age