

TEMAS DE REVISÃO

MANAGEMENT OF LARYNGEAL CARCINOMA

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INTRODUCTION

Cancer of the larynx in North America is the commonest form of cancer of the head and neck region. In our own institution it accounts for one-quarter of all head and neck cancers¹. The purpose of this article is to review the management of this condition with particular emphasis on the relative roles of radiation and surgery.

A) GLOTTIC CANCER

INTRODUCTION:

In North America glottic cancer is the commonest form of laryngeal carcinoma representing approximately 75% of all cases of cancer of the larynx. The staging system used in this article is the one put forward by the UICC and is shown in Table 1. In our experience Stage T1N0 is the commonest type of glottic carcinoma being approximately 50% of all glottic tumors. Stage T2N0 is 25%, T3N0 12%, T4N0 8% and nodal disease is present in 5% of patients with glottic carcinoma. In addition even in advanced stage disease nodal disease at presentation or subsequently following treatment is rare and therefore management generally is aimed primarily at the tumor in the larynx.

MANAGEMENT POLICY AND PHILOSOPHY:

Our general management policy and philosophy for the treatment of glottic carcinoma is to use primary moderate dose radiotherapy for all stages of disease², reserving surgery for biopsy proven residual or recurrent tumor 3 months or more after completion of irradiation. The rationale of this management policy is to preserve the larynx where possible without prejudicing the cure rate of the tumor.

TABLE 1 – UICC STAGINS SYSTEM FOR GLOTTIC CARCINOMA

| | |
|-----|--|
| T1a | tumor confined to one vocal cord with normal mobility. |
| T1b | tumor confined to both vocal cords with normal mobility. |
| T2 | tumor extending to either the subglottic or supraglottic regions with normal or impaired mobility. |
| T3 | tumor limited to the larynx with fixation of one or both cords. |
| T4 | tumor extending beyond the confines of the larynx. |
| N0 | regional nodes not palpable. |
| N1 | movable homolateral nodes. |
| N2 | movable contralateral or bilateral nodes. |
| N3 | fixed nodes. |
| M0 | no evidence of distant metastases. |
| M1 | distant metastases. |

Moderate dose radiotherapy is employed with careful attention to radiotherapy technique. Doses used are in the range of 5000 rads in 4 weeks in 20 fractions, 5500 rads in 5 weeks in 24 fractions and 6000 rads in 6 weeks in 30 fractions.

THE ADVANTAGES OF MODERATE DOSE RADIOTHERAPY ARE FIVE-FOLD:

1. Major radiotherapy complications (such as laryngeal necrosis) are minimized.
2. The complication rate associated with surgery in those failing irradiation is kept within an acceptable range and permits conservative voice preserving procedures to be carried out in suitable cases.
3. It minimized post irradiation oedema, facilitating early diagnosis of residual or recurrent disease therefore allowing high control rates to be obtained with surgical salvage.

4. It optimizes voice quality.

5. The local and regional control rate of the tumor is not jeopardized by the use of these moderate doses.

In order for the management policy of radical radiotherapy with surgery for salvage to be successful, it is essential that the failures of irradiation be recognized early to permit successful surgical retrieval of the irradiation failures. The majority of recurrences occur in patients with advanced primary tumors (T3, T4) within the first 6 months following treatment¹. Therefore close follow-up in the first year following irradiation at monthly intervals is essential. In those patients who are at high risk of recurring following irradiation (T2 with impaired mobility, T3 and T4 cases) it is now our policy to routinely carry out direct laryngoscopy and biopsy 3 months after the completion of irradiation. If positive histology is obtained surgery is carried out.

SELECTION OF PATIENTS FOR TREATMENT:

Virtually all patients with glottic carcinoma are treated with primary radical radiation with surgery in reserve. For reasons to be discussed later in detail we do not regard the presence of subglottic extension, anterior commissural involvement, a fixed vocal cord, laryngeal cartilage involvement, the presence of nodal disease, or an obstructive larynx requiring tracheostomy as a contra-indication to the use of this policy of management¹.

TECHNIQUES OF TREATMENT:

Strict and careful attention to radiotherapy technique is very important in the use of radiotherapy for glottic carcinoma³. We routinely immobilize the patient with a plastic mask or plaster cast. Patients are generally treated with megavoltage irradiation employed cobalt 60. The technique of treatment is particularly important in T1 glottic cancer where the local recurrence rate of tumor was reduced from 18

to 9% with the increase in radiation field size from 5x5 to 6x6cm. in size. Similarly in T1 glottic cancer it is vital to make sure that the anterior commissural region receives the full dose of radiotherapy. Since this region is very close to the skin surface, bolus or plastic is placed over this region so full dose build-up occurs. In our experience when careful attention to radiotherapy technique is used, the involvement of the anterior commissure has no effect on our ability to locally control the tumor¹.

For patients with subglottic disease a technique called the angled down wedge pair technique has been developed and used for the past 15 years³. This technique gives homogeneous irradiation down to the level of the carina (if necessary) from two lateral fields. With the use of laryngeal tomography delineating the extent of subglottic extension combined with the use of this radiation technique we have not found that subglottic extension influences our ability to cure T2⁴ or T3 glottic cancer.

MANAGEMENT OF GLOTTIC CANCER:

a) Carcinoma in situ (UICC TISNOMO):

Carcinoma in situ of the larynx is a histopathologic rather than a clinical entity⁵. It is unclear what proportion of patients with carcinoma in situ of the larynx will ultimately develop invasive carcinoma. The management of this form of glottic carcinoma is controversial between the advocates of surgery employing endolaryngeal microscopic stripping of the vocal cord⁵ or primary radiotherapy with surgery in reserve. A significant proportion of patients treated surgically require repeat stripping for recurrence. The results of radiotherapy for carcinoma in situ of the larynx is shown in Table 2^{1, 6, 7}. In all the series shown in Table 2 the doses of radiotherapy used were the same as that used for invasive carcinoma. The overall control rate is very high (83 to 94%) and very few patients die of laryngeal carcinoma. Radiotherapy is therefore a highly effective method

TABLE 2 – RESULTS OF RADIOTHERAPY FOR CARCINOMA IN SITU OF THE LARYNX TREATED IN LARGE CENTRES

| SERIES | NO. OF PATIENTS | LOCAL CONTROL BY RADIOTHERAPY | % DEAD LARYNX CANCER |
|---|-----------------|-------------------------------|----------------------|
| PRINCESS MARGARET HOSPITAL ¹ | 92 | 94% | 0 |
| M. D. ANDERSON HOSPITAL ⁶ | 86 | 89% | 0 |
| MASSACHUSETTS GENERAL HOSPITAL ⁷ | 67 | 83% | ? |

of treatment for carcinoma in situ of the vocal cords and we recommend it as primary treatment in all cases following stripping of the vocal cord with the exception of those cases in whom there is only a small area of carcinoma in situ change in the middle of the vocal cord which has been completely removed by the surgical procedure.

b) Invasive Carcinoma Stage T1N0 and T2N0:

It is generally accepted that irradiation treatments are the initial treatment of choice for invasive carcinoma confined to the vocal cord. This is because of the superior quality of voice obtained using irradiation compared to partial laryngectomy. The results of radiotherapy in more than 1500 patients treated in large North American Centres for T1 glottic cancer is shown in Table 3. It can be seen that the local control rate by irradiation is approximately 90% with one-half to two-thirds for the post radiotherapy recurrences being saved by subsequent surgery. A significant fraction of the failures (one-third to one-half) can be salvaged by partial laryngectomy with preservation of laryngeal speech. There are few problems with carrying out a partial laryngectomy on patients previously irradiated for T1 glottic cancer provided that moderate doses of radiotherapy are used.

There is little evidence in T1 glottic cancer to support the uses of doses in excess of 6000 rads in 6 weeks. Our recommendations for the optimal radiotherapeutic treatment of T1 glottic cancer is a dose of 5000 rads in 4 weeks in 20 fractions or 6000 rads in 6 weeks in 30 fractions

using a minimum field size of 6x6cm in size. This will optimize both the control rate of the tumor and the functional quality of the voice.

T2 glottic cancer takes in quite a wide spectrum of disease from a small tumor of the vocal cord with minimal extension to the laryngeal ventricle to a very large tumor involving both sub and supraglottic larynx with impairment of mobility of the vocal cord. The results of radiotherapy with surgery in reserve for T2 glottic cancer are shown in Table 4. The local control rate by irradiation varies between 60 to 74% and between one-half to two-thirds of the radiation failures are controlled by subsequent surgery which generally consists of a laryngectomy. We have not had much success salvaging patients with T2 glottic cancer with a partial laryngectomy. The proportion of patients who die of laryngeal cancer in this stage grouping is small varying between 6 to 16% in the large reported series. These results are comparable to the results obtained with primary surgery and the functional results of treatment in patients successfully irradiated is superior.

The two most important factors which influence the ability of irradiation to control T2 glottic cancer is the presence or absence of impaired mobility of the vocal and the patients sex. Patients with T2 glottic cancer with impaired mobility of the vocal cord have a control rate by irradiation between 54-58% (similar to T3 glottic cancer) as compared to 77-78% in patients who have normal mobility of the vocal cord¹. The influence of sex on the ability of

TABLE 3 – RESULTS OF RADIOTHERAPY T1 GLOTTIC CANCER

| SERIES | NUMBER OF PATIENTS | LOCAL CONTROL BY RADIOTHERAPY | % DEAD LARYNX CANCER |
|---|--------------------|-------------------------------|----------------------|
| PRINCESS MARGARET HOSPITAL ¹ | 571 | 87% | 6 |
| MASSACHUSETTS GENERAL HOSPITAL ⁶ | 723 | 90% | 3 |
| M. D. ANDERSON HOSPITAL ⁷ | 332 | 89% | 2 |

TABLE 4 – RESULTS OF RADIOTHERAPY T2 GLOTTIC CANCER

| | LOCAL CONTROL BY RADIOTHERAPY | % DEAD LARYNX CANCER |
|---|-------------------------------|----------------------|
| PRINCESS MARGARET HOSPITAL ¹ | 68% | 16 |
| MASSACHUSETTS GENERAL HOSPITAL ⁶ | 69% | 14 |
| M. D. ANDERSON HOSPITAL ⁷ | 74% | 6 |

irradiation to control glottic cancer is shown in Table 5. In every stage grouping women have a superior control rate to men. The reason for this is unclear but others have not a similar relationship⁷. It is our strongly held belief that irrespective of the stage of tumor all women with glottic cancer should be primarily irradiated.

We have not found that the presence or absence of subglottic extension influences our ability to control T2 glottic cancer⁴. This is attributed to the technique of radiation that we use (angled down wedge pair technique) and the careful assessment of the presence or absence of subglottic extension using laryngeal tomography.

T3 GLOTTIC CANCER

This is the area of greatest controversy in the treatment of glottic carcinoma between the advocates of primary surgery with or without pre or post operative irradiation and the advocates of radiation with surgery in reserve.

In Toronto and a number of other centres we have preferred to use radiation with surgery in reserve. The results of radiotherapy with surgery in reserve in centres where radiation was the preferred modality of initial treatment is

shown in Table 6. In those centres where the majority of patients were managed by radiation initially, the control rate by irradiation (with the exception of Wang) was approximately 50%. In contrast in the surgical literature the results of radiotherapy for T3 glottic cancer are much poorer, this is illustrated in Table 7. It can be seen that only very small numbers of patients in these surgical series were irradiated (6-23% of the total numbers of cases of T3N0 glottic cancer seen in these institutions) and the results of such irradiation are quite poor. Since surgery was the preferred initial treatment option for T3 glottic cancer in these centres it is quite apparent that only candidates who were not fit enough for surgery were irradiated and therefore the poor results can be explained on the basis that only selected unfavorable patients were irradiated.

When two methods of treatment produce similar cure rates then one of the major factors determining which method of treatment is chosen is the quality of life¹⁴. Therefore irradiation with surgery in reserve is the preferred option of treatment for T3 glottic cancer because of its potential for saving the larynx and laryngeal speech compared to primary surgery which would generally consist of a total laryngectomy, provided that survival is not prejudiced by

TABLE 5 – RESULTS OF RADIOTHERAPY IN MALES AND FEMALES WITH GLOTTIC CANCER

| | % LOCAL CONTROL BY RADIOTHERAPY | |
|------|---------------------------------|--------|
| | MALE | FEMALE |
| T1N0 | 87 | 97 |
| T2N0 | 68 | 87 |
| T3N0 | 46 | 75 |

TABLE 6 – RESULTS OF RADIOTHERAPY T3 GLOTTIC CANCER
"RADIOTHERAPY CENTRES"

| SERIES | NO. OF PATIENTS | % LOCAL CONTROL RT | % CASES TREATED BY RT |
|-----------------------|-----------------|--------------------|-----------------------|
| HARWOOD | 150 | 51 | 77 |
| STEWART ⁹ | 67 | 57 | 80 + |
| WANG ⁷ | 65 | 32 | 65 |
| TROTT ¹⁰ | 300 + | 50 | NA |
| LEDERMAN ⁸ | 289 | 47 | 80 + |

**TABLE 7 – RESULTS OF RADIOTHERAPY T3 GLOTTIC CANCER
"SURGICAL CENTRES"**

| SERIES | NO. OF PATIENTS | % CONTROL BY RT | % CASES TREATED BY RT |
|--------------------------|------------------------|----------------------------|----------------------------------|
| SKOLNICK ¹¹ | 8 | 25 | 6 |
| KIRCHNER ¹² | 4 | 25 | 13 |
| MARTENSSON ¹³ | 16 | 19 | 23 |

using irradiation initially. Table 8 shows the survival data and proportion of survivors who possess their larynx in patients treated primarily by surgery (500 + patients) and a group of more than 700 patients treated by irradiation with surgery in reserve. It can be seen that there is no difference in terms of survival between those treated primarily by surgery and those treated by irradiation with surgery in reserve. The major difference between the two groups of patients is in the proportion of survivors who possess their larynx and natural voice. Approximately 60% of the irradiation series survivors possess their entire larynx compared to less than 10% of the surgical series. Therefore in experienced hands radiation with surgery in reserve is an acceptable method of treatment for T3 glottic cancer. In order for irradiation with surgery in reserve to be successful a number of criteria must be strictly adhered to:

1. Moderate doses of irradiation should be

used. The reasons for this are documented previously in the introductory segment.

2. The patient has to be prepared to come for close follow-up on a monthly basis in the first year following irradiation. The reasons for this are again documented in the introductory segment.

The Mayo Clinic has recently become a major advocate for primary surgery in T3 glottic cancer. The surgical results obtained by the Mayo Clinic are superior to those obtained and illustrated in Table 8¹⁷. There are a number of reasons for this:

1. Referral bias. The Mayo Clinic is situated in a small town with a small population base, therefore the majority of patients coming for treatment at the Mayo Clinic come from outside of Rochester Minnesota. Therefore patients have to be well enough to travel to get treatment at the Mayo Clinic. This is reflected in the type of patients seen at the Mayo Clinic with T3 glottic

TABLE 8 – SURVIVAL AND VOICE PRESERVATION T3 GLOTTIC CANCER

| PRIMARY SURGERY | % ALIVE | % SURVIVORS WITH LARYNX |
|--|----------------|------------------------------------|
| KIRCHNER ¹² | 60 | 6 |
| SKOLNICK ¹¹ | 48 | 3.5 |
| VERMUND ¹⁵ | 61 | NA |
| OGURA ¹⁶ | 60 | NA |
| RADIATION WITH SURGERY IN RESERVE | | |
| HARWOOD | 55 | 66 |
| LEDERMAN ⁸ | 45 | 63 |
| WANG ⁷ | 57 | 57 |
| STEWART ⁹ | 57 | 57 |
| VERMUND ¹⁵ | 50 | 66 |

cancer. Ninety of 106 patients seen there with T3 glottic cancer had tumor confined to the vocal cord, ventricle and area less than 10mm below the cord. In contrast in our own experience and that of others this is an extraordinarily high proportion of patients with limited tumors, the majority of patients seen in our institution with T3 glottic cancer have extensive sub and supraglottic extension.

2. Staging bias. The patients reported in Tables 7 and 8 with T3 glottic cancer are clinically staged, in contrast the series reported by Mayo are pathologically staged based on the findings of laryngectomy. Since it has been clearly shown by Kirshner¹⁸ that approximately one-third of clinical T3 tumors are pathologically T4 it is quite apparent that Mayo results cannot be compared with other centres results because of the staging and referral bias referred to above.

T4 GLOTTIC CANCER

Our experience with the treatment of T4 glottic cancer is relatively limited. We have not found that thyroid cartilage involvement represents a contra-indication to the use of irradiation. The survival using radiation with surgery in reserve for patients with T4 glottic cancer is 49% at 5 years, a similar result to that obtained in surgical series (54%, 5 years survival).

B) SUPRAGLOTTIC CANCER

INTRODUCTION:

Supraglottic cancer in our experience represents approximately one-quarter of all cancers of the larynx. The proportion of glottic to supraglottic carcinomas varies quite substantially throughout the world probably related to the level of consumption of alcohol. In Italy for example, supraglottic carcinoma is more common in proportion to glottic cancer than in North America.

Supraglottic cancer is a more serious disease than glottic cancer, it more frequently presents with advanced stages at the primary site and also nodal metastases are much more prevalent than

in primary glottic cancer. In addition twice as many patients with supraglottic cancer die of intercurrent disease compared to glottic cancer patients. This is principally due to a large increase in the incidence of second primary cancers in the respiratory tract.

Since nodal disease is an important component of supraglottic carcinoma management must take greater account of treating the regional lymph nodes than is the case with glottic carcinoma. The staging system used for supraglottic carcinoma is the UICC staging system (Table 9).

MANAGEMENT POLICY AND PHILOSOPHY:

Our general management policy and philosophy for the treatment of supraglottic carcinoma is similar to that developed for glottic carcinoma. Virtually all patients with supraglottic carcinoma are treated with primary moderate dose radiation with surgery in reserve, this includes patients with Stage T3 or T4 disease or those patients presenting with nodal disease. Nearly all patients presenting to us with supraglottic carcinoma are treated with the angled down wedge pair technique since this is a good method of treating all of the cervical lymph nodes. We regard it as essential in the management of all supraglottic carcinomas that all the deep cervical lymph nodes be included in the treatment volume even for patients with small T1 tumors.

EARLY SUPRAGLOTTIC CANCER (CLINICAL STAGE T1, T2N0):

The principal controversy in the management of early supraglottic cancer is between the advocates of irradiation with surgery in reserve¹⁹ and those that advocate primary surgery. Primary surgery for early supraglottic carcinoma consists of horizontal supraglottic laryngectomy with or without bilateral neck dissection for selected cases, or total laryngectomy with or without neck dissection for those cases not suitable for conservative surgery.

The principal proponents of conservative surgery for early stage supraglottic carcinoma has been the St. Louis group and the group at the

TABLE 9 – UICC STAGING SYSTEM FOR SUPRAGLOTTIC CANCER

| | |
|----|---|
| T1 | tumor confined to the supraglottic larynx without fixation |
| T2 | tumor invading the glottic larynx without fixation |
| T3 | tumor confined to the larynx with fixation of the larynx |
| T4 | tumor extending outside of the larynx (commonly pre-epiglottic space, base of tongue hypopharynx) |

Mayo Clinic. As previously discussed¹⁹ these two groups see very selected patients from all over North America with very small tumors and the impressive results obtained by this procedure in these centres can be partially explained on the basis of referral bias.

Our own experience in Toronto with horizontal supraglottic laryngectomy on an unselected group of patients was far less favourable with a high recurrence rate being observed in the pre-epiglottic space, vallecula and base of tongue and also a high recurrence rate in the neck nodes bilaterally. In view of our extremely favourable results both in terms of cure and function employing irradiation with surgery in reserve we prefer this option for the management of T1 and T2N0 supraglottic carcinoma.

Between 1960 and 1979 we saw 136 patients with T1 and T2N0 supraglottic carcinoma who were treated with radical radiotherapy with surgery in reserve. The survival data, local and regional control rates of the tumour during this 20 year time period are shown in Table 10. It is important to realize that this is clinically staged material and that a significant proportion of these patients clinically staged T1 or T2N0 would have been pathological Stage T4 or would be node positive.

TABLE 10 – DATA ON T1 AND T2 N0 SUPRAGLOTTIC CANCER

| | T1N0 | T2N0 |
|------------------------------|------|------|
| ALIVE AT 5 YEARS | 53 | 52 |
| DEAD SUPRAGLOTTIC CANCER | 21 | 22 |
| DEAD INTERCURRENT DISEASE | 24 | 26 |
| LOCAL CONTROL BY IRRADIATION | 78 | 67 |
| REGIONAL CONTROL | 89 | 82 |

In addition we have analyzed the results of irradiation with surgery in reserve by time period and technique of treatment and this is shown in Table 11. It can be seen that there has been a substantial improvement in the results of treatment during the time period of the study with a significant reduction in the proportion of patients dying of tumor during the most recent time period. This is due primarily to a significant and major reduction in the proportion of patients recurring in the initially clinically negative neck. This is attributable to the use of larger irradiation field sizes such that the entire

upper, middle and lower deep cervical lymph nodes are included within the irradiation volume. As a result of increasing the irradiation field size from treatment to the primary alone (7x7cm in size or less) to the entire neck (greater than 7x7cm in size) the frequency of recurrence in the neck fell from 19 to 3%. We believe therefore that it is vitally important in the treatment of early supraglottic carcinoma that the regional neck nodes be included within the treatment volume.

TABLE 11 – RESULTS OF TREATMENT OF EARLY SUPRAGLOTTIC CANCER VERSUS TIME

| | 1960-69 % | 1970-74 % | 1975-79 % |
|---------------------------------|--------------|--------------|--------------|
| LOCAL CONTROL BY IRRADIATION | 69 | 56 | 84 |
| REGIONAL CONTROL BY IRRADIATION | 71 | 88 | 96 |
| % DEAD SUPRAGLOTTIC CANCER | 30 | 25 | 5 |

ADVANCED SUPRAGLOTTIC CANCER (STAGE T3N0, T4N0, NODE POSITIVE):

The management of advanced supraglottic cancer is difficult and the results of treatment less satisfactory. Many of these patients present with advanced nodal disease combined with large primary tumors, are frequently in poor general condition which complicates the decision about management in these patients.

A comparison of the results of treatment of advanced supraglottic carcinoma in our institution comparing radiation with surgery in reserve and high dose pre-operative irradiation and surgery revealed no difference in terms of survival or proportion of patients dying of tumour¹. For this reason we continue to advocate the use of irradiation with surgery in reserve for advanced supraglottic cancer. The results of this management policy in terms of survival and proportion of patients dying of supraglottic carcinoma, local and regional control rates by irradiation for the common stage groupings are shown in Tables 12 and 13. It can be seen that survival is significantly worse with the development of nodal disease and the development of fixation of the nodal disease (N3) stage grouping.

TABLE 12 – SURVIVAL DATA ADVANCED SUPRAGLOTTIC CANCER

| | % ALIVE 5 YEAR | % DEAD LARYNGEAL CANCER |
|------------|-------------------|-------------------------------|
| T3N0, T4N0 | 42 | 34 |
| N1 | 27 | 53 |
| N3 | 13 | 71 |

TABLE 13 – LOCAL AND REGIONAL CONTROL BY IRRADIATION ADVANCED SUPRAGLOTTIC CANCER

| | LOCAL CONTROL BY IRRADIATION % | REGIONAL CONTROL BY IRRADIATION % |
|------------|---|--|
| T3N0, T4N0 | 54 | 90 |
| N1 | 53 | 56 |
| N3 | 45 | 39 |

The local control rate by irradiation for the T3 and T4N0 cases is similar to glottic carcinoma cases with equivalent stage grouping.

However, it is quite apparent that the results of treatment of advanced supraglottic carcinoma are unsatisfactory. We therefore, initiated a pilot study employing 5FU infusion, Mitomycin C and irradiation in this subgroup of patients. The results of the pilot study was sufficiently encouraging that we have undertaken a major randomized controlled clinical trial comparing radical radiation with surgery in reserve to 5FU infusion, Mitomycin C, and, split course irradiation. The endpoints of this trial are the local and regional control rate of the tumor and to reduce the laryngectomy rate in this group of patients, as well as trying to improve the survival in this advanced group of patients.

In summary therefore, our policy for patients with cancer of the larynx is to use irradiation

with surgery in reserve. We believe that this produces equivalent survival to primary surgery even in advanced cases but superior quality of life.

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