

The Heterogeneity of T2NO Glottic Carcinoma Treated by Irradiation

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During a ten-year period from 1978 through 1987, 44 patients with T2NOMO glottic cancer were treated with radical radiation therapy at the Yonsei University Medical Center. Forty-two patients had a minimum follow-up of 3 years, and 81% had at least five years of follow-up. Patients were staged according to the AJCC system. Forty-two patients have been analyzed in detail with respect to two variables: the status of vocal cord mobility and the degree of local extension of the disease. Five-year local recurrence free survival rates were as follows: All 42 patients, 53.3%; patients with normal vocal cord mobility (n=18), 69.1% versus patients with impaired vocal cord mobility (n=24), 43.4% (p<0.05); patients with subglottic extension (n=15), 36.7% versus patients without subglottic extension (n=29), 61.9% (p<0.05). The most favorable prognostic group included the patients with normal mobility without subglottic extension (n=14), 83.1%.

On the basis of this analysis, we confirmed the presence of heterogeneity in T2NOMO glottic cancer. This study indicates that further randomized controlled trials are warranted to evaluate individualized treatment according to its heterogeneity.

Key Words: Glottic cancer, T2NO stage, Radiotherapy

INTRODUCTION

Squamous cell carcinomas arising from one or both vocal cords and/or the anterior commissure are included in the category of glottic carcinoma. These tumors may spread supraglottically, involving the laryngeal ventricle, as well as subglottically. Early glottic cancer comprises a group of very heterogenous diseases with the tumor confined to the vocal cords in Stage I disease and with supraglottic and/or subglottic involvement with normal or impaired mobility in Stage II disease. Many studies demonstrate that glottic cancer, limited to the vocal cord (T1), has an excellent prognosis with radiotherapy; cure rates are very high and in about 90% of patients the larynx can be preserved. The rare local failures can be controlled with rescue laryngectomy, and in some selected patients, even limited surgery remains possible after irradiation¹⁻⁴. Is T2 glottic cancer an early cancer? The T2 group in glottic cancer, defined as a "tumor confined to the larynx which extends to supraglottis and/or subglottis, and/or with impaired cord mobility" by AJCC (American Joint Committee On Cancer), has var-

ious local control rates for different selected groups from about 40%⁵) to about 80%⁶).

Between early and advanced cancer lies the T2NOMO for which no single treatment has gained universal popularity among physicians. This retrospective study attempts to make an in-depth study on the probable heterogeneity of the T2 glottic cancer in relation to the local control probability, local recurrence free survival rates on one side and the extent of the primary tumor and the mobility of the vocal cord on the other.

METHODS AND MATERIALS

1. Patients

A total of 44 patients were treated by radical radiotherapy for T2 glottic carcinoma from 1978 through 1987 and two cases did not allow a sufficient accurate evaluation for the results of treatment; so these 2 patients were omitted from the study. Forty-two patients had a minimum 3-year follow-up and 81% had at least five years of follow-up. All 42 patients were 36-73 years of age (mean age:53). Most of them (40/42) were men. All cases were squamous cell carcinoma, and their differentiation was reviewed. Unilateral involvement was noted in 32 patients. The locations of the lesion varied. The most common location was the

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anterior two thirds (26/42) and diffuse infiltrations were also noted (14/42). The lesions were staged according to the system recommended by the AJCC. All patients were staged after clinical, endoscopic and radiologic examinations including tomography. Some patients underwent laryngography.

The 42 patients staged T2NOMO were analyzed with respect to two variables: the status of vocal cord mobility and the degree of local extension of the disease. Local recurrence of disease and death from cancer of the larynx were employed as end-points of this analysis. The basic method of treatment for these patients has been radical radiation with salvage surgery for persistent or recurrent disease. In terms of tabulating local extension of disease, since all tumors of the glottic portion of the larynx by definition arise from the vocal cord, it was not considered to be a site of extension. Single sites of extension included the subglottis alone, ventricle and false cords (considered as one site together), and all other regions within the supraglottic larynx, each recorded as a separate site: posterior surface of suprahoid epiglottis, (including the tip), aryepiglottic fold, arytenoid, and infrahyoid epiglottis. Involvement of the same site on both sides of the glottic larynx was recorded as two sites. Mobility was considered impaired if any impairment of mobility of the vocal cord was noted on clinical examination, tomography or laryngography. (The patient was excluded if the vocal cord or larynx was totally fixed, i.e., stage T3NO).

Actuarial local recurrence free rates and actuarial survival rates were calculated by Kaplan-Meier methods. Patients in whom local or cervical control was not achieved were considered immediate recurrences for the purposes of this analysis. P values are calculated in actuarial analysis by the method of log rank test.

2. Irradiation: Dosage and Technique

Most patients were treated with cobalt-60 irradiation (40/42), using a total dose of 6000 ~7000 cGy in 6~8 weeks. Parallel opposed two lateral fields were ordinarily used. If the tumor extended into or only involved the posterior half of the cord, most patients had the addition of a wedge filter. Patients with subglottic extension had the addition of anterior lower neck port. The dose per fraction was 200 cGy per day. The upper margin of the field was generally the midthyroid notch; in patients with supraglottic extension, the margin was enlarged upward. The inferior border always

included the entire cricoid cartilage and was lowered when subglottic extension was found. The posterior border depended upon the extent of the lesion with generous margin. The anterior lower neck irradiation was used in patients with subglottic extension case by case. The field size ranged from 6×6 cm² to 10×13 cm². The mean irradiated volume was 83 cm³. Field reductions were made for the last five or six treatments when possible. The neck nodes were not included routinely. The total dose on mid-depth ranged from 6000 to 7000 cGy with 200 cGy per fraction. The mean dosage was 6500 cGy.

RESULTS

Of 42 patients with T2NOMO glottic carcinoma, we analyzed their prognostic factors according to the presence of impaired vocal cord mobility and the local extension of cancer. Actuarial local recurrence free survival rates were employed as end-points of this analysis. We also tried to evaluate the dose-time relationship in T2 glottic cancer and the role of salvage operation in locally failed patients after full dose irradiation.

1. Overall Survival and Local Recurrence Free Survival

Actuarial overall survival and local recurrence free survival of 42 patients by radical radiation treatment is shown in Fig. 1. The five year actuarial survival rate was 63.1% and local recurrence free survival was 53.3%. There were recurrences among the 42 patients; 14 Local control failure, 1 nodal, 1 distant metastasis to lung. Most of the patients who recurred locally did so within 24 months after radical radiation treatment (12/14).

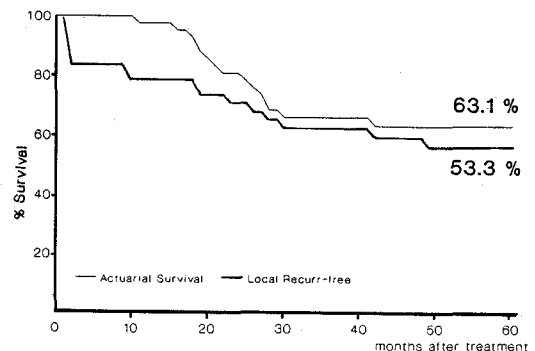


Fig. 1. Actuarial survival and local recurrence free survival rate of T2NOMO glottic cancer patients.

2. Comparison of the Local Control Rate in Terms of Significant Prognostic Tumor-Related Factors

Fig. 2 shows the local control rates of the patients with mobile vocal cord and impaired vocal cord mobility. The 5 year local recurrence free survival rate of 18 patients with normal vocal cord mobility was 69.1% and with impaired vocal cord mobility was 43.4% ($p < 0.05$). Fig. 3 shows the local control rates of the patients with subglottic extension and without subglottic extension. The 5 year local recurrence free survival rates were 61.9% and 36.7% respectively ($p < 0.05$). Table 1 summarizes the differences of local control rates by local extension of glottic cancer. A comparison for all categories of local extension of the tumor led to a different probability of local control with radiotherapy, but this difference is not statistically significant. Normal mobility of vocal cord, without extension of the tumor to the subglottic lesions, was readily controlled with radiation alone (83.1%), but this was seen in only 14 patients. The patients with subglottic extension or impaired mobility of

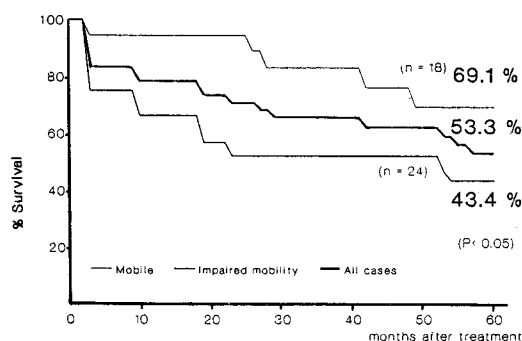


Fig. 2. Local recurrence free survival rate: mobile vs impaired cord mobility.

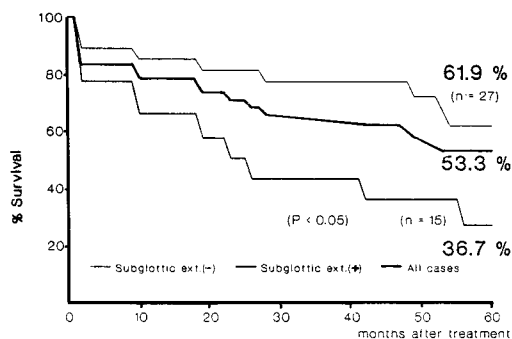


Fig. 3. Local recurrence free survival rate: subglottic extension (+) vs subglottic extension (-).

vocal cord had unfavorable outcome within the T2 stage glottic cancer group, since 5 year local recurrence free survival rates were under the 50%. (Table 2, Fig. 4)

3. Dose-Response Relationship

A minimum dose of 60 Gy has been used for apparently small, radiosensitive tumors. Higher

Table 1. Five Year Local Recurrence Free Survival Rate by Local Extension

Local Extension	No. of patients	Local Recurrence free survival (%)
Subglottis only	8	57.1
Ventricle ± FC	20	70.6
Bilateral (+ SE or FC)	7	38.1
More than 3 sites	7	14.3
Total	42	53.3

Table 2. Five Year Local Recurrence Free Survival Rate by iMobility and Subglottic Extension

Subglottic extension	iMobility		
	Normal	Impaired	Total (%)
Subglottis (-)	83.1 (n=14)	47.9 (n=13)	61.9 (n=27)
Subglottis (+)	25.0 (n= 4)	40.4 (n=11)	36.7 (n=15)
Total	69.1 (n=18)	43.4 (n=24)	53.3 (n=42)

Numbers in parentheses are the number of cases in each category

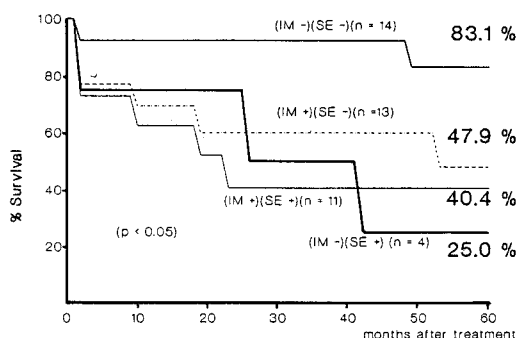


Fig. 4. Local recurrence free survival rate by vocal cord mobility and subglottic extension.

dosages (up to 70 Gy) with shrinking fields have been delivered to the tumors with restricted mobility and/or with greater volume, particularly when the regression pattern of the tumor was not satisfactory during radiotherapy. Relation between dose level and response to irradiation cannot be demonstrated from this study. Since patients with T2 glottic lesions received higher doses, there were a number of different tumors at different dose levels. Individualized tailored treatment techniques appear to have achieved better results for the worse T2 glottic cancers in this study.

4. Surgical Salvage

Surgical salvage was attempted in 4 patients

Table 3. Results of Radiation Treatment in T2 Glottic Cancer with Impaired Mobility-Review

Author	No. of patients	Results (%)
Martensson et al ¹⁸⁾	19	47*
Wang ⁶⁾	45	64*
Kun and van Angel ¹⁹⁾	43	58+
Quayum et al ²⁰⁾	60	57≠
Harwood and De Boer ⁷⁾	52	51 §
Bogaert et al ¹⁰⁾	28	65 §
This study	24	44 §

* 5 year determinate recurrence-free rate (intercurrent deaths and cases lost to follow-up excluded).

+ 3 year determinate recurrence-free rate.

≠ 5 year crude survival.

§ 5 year actuarial local recurrence-free rates (intercurrent deaths and patients lost to follow-up included for the time of observation).

with resectable recurrences. One patient with recurrent T2 glottic lesion was salvaged successfully by a hemilaryngectomy and neck dissection. Salvage was unsuccessful in 3 patients undergoing total laryngectomy. All three patients died within 12 months.

DISCUSSION

It is generally accepted that early glottic cancer responds well to radiation therapy with 5-year cure rate of 85-90%^{2,3)}. But the T2 group in glottic cancer has been defined as "a tumor confined to the larynx with extension to either the supraglottis or the subglottis regions with normal or impaired mobility" is a rather heterogenous group of tumors evidenced by the different ranges of local control rates following primary radiotherapy. The local control rates for different selected groups vary from 40%⁵⁾ to 80%⁶⁾.

Part of the rationale for a staging system is to permit, within a particular disease site, a separation of groups of patients with different prognoses. As a result of this separation of groups, it is possible to predict more accurately the outcome of treatment and, in subgroups which do badly, to develop new treatment strategies. In glottic cancer, the group of patients in the T2 Stage is the most heterogenous; this group could include a patient with a small tumor of the vocal cord with 1-mm extension into the subglottic or supraglottic region or alternatively a huge tumor involving the subglottic and supraglottic regions extensively combined with impaired mobility of the vocal cord. Several authors extensively combined with impaired mobility of the vocal cord. Several authors have emphasized the impor-

Table 4. Stage II Glottic Carcinoma Literature Review, Local Control Probability % with Primary Radiotherapy

Author	Year	Normal mobility	Impaired mobility	Tumor dose/weeks/fraction dose
Horiot et al. ⁵⁾	1972	80 (109)*	39 (18)+	60-70Gy/5.5-6.5/2.2Gy
Karim et al. ⁸⁾	1980	80 (40)	73 (19)≠	66-76Gy/6.5-7.5/2Gy
Harwood and De Boer ⁷⁾	1980	77 (93)	52 (52)	50Gy/4/2.5Gy
Fletcher ²¹⁾	1980	77 (108)	61 (41) §	60-70Gy/5.5/2.2Gy
vd Bogaert et al. ¹⁰⁾	1983	62 (33)	65 (28)	40-70Gy/4-7/2Gy
wang ⁶⁾	1983	78 (97)	58 (76)	65-70Gy/6.5-7/2Gy
Karim et al. ¹⁶⁾	1986	81 (121)	79 (45)	68-74Gy/7-7.5/2Gy
this study	1990	69 (18)	44 (24)	60-70Gy/6-7/2Gy

* Perhaps a few patients with impaired mobility were also included.

+ With large volume.

≠ Volume also analyzed.

§ Large volume.

No. of patients in parenthesis.

tance of this distinction and some have proposed to subdivide T2 in T2A (local extension) and T2B tumor (impaired mobility), where T2A would have a prognosis close to T1 lesions and T2B tumors would have an outcome closer to T3⁷⁻¹¹.

We undertook an analysis of our patients with T2NOMO glottic cancer to see if it was possible to further delineate into separate groups. The basic reason for this analysis was to see if separation was possible to aid in designing therapeutic options for a prospective trial on cancer of the larynx that we are initiating. It is quite clear from the results in terms of local recurrence free survival rates with radiotherapy in this staging grouping.

1. Local Extension and Cord Mobility

Many authors reported that the high risk factors appear to be associated with impaired mobility of the cord and the volume of the tumor as indicated by its growth in the vertical and/or the transverse direction⁷⁻⁹. The relatively poor prognosis for this group, as far as we can gather from literature, is shown in Table 3¹⁰. In the literature review, the high risk factors of tumor volume or extension and impaired mobility have not been clearly separated. In two studies the authors indicated the worse prognosis (55% and 39% local control probability) occurred when impaired mobility was associated with extensions of the tumor beyond the cord^{5,10}.

However Harwood et al insisted that mobility of vocal cord appears to be a more important prognostic factor by their local control comparison adjusted for local extension. They reported that, though there was a trend in favor of poorer local control rates and prognosis in the more extensive tumors in terms of local horizontal and vertical superficial spread of disease involving three or more sites, the difference was not statistically significant when correction was made for the effect of impaired mobility⁷. The vertical spread of a glottic carcinoma that involves the supraglottic or subglottic regions alters a biologic behavior of the tumor by making available to it new routes of indirect and lymphatic spread and worsens the prognosis. This is reflected in a decreased survival rates with both radiotherapy and surgery. Olofsson et al observed that eight laryngectomy specimens with prelaryngeal node metastasis all had subglottic involvement by tumor, with six showing extension into the cricothyroid membrane¹¹. Analysis of the treatment results of 125 glottic carcinomas with subglottic extension by Sessions and others revealed 3-year survival rates of 63% with radio-

therapy¹².

These authors correlated the ability to obtain tumor control with the extent of the lesion. The survival for unilateral cord lesion involving anterior commissure and having less than 10 mm of subglottic extension was 90%, but dropped to 50% with more than 10 mm of subglottic spread. But Harwood demonstrated that the presence or absence of subglottic extension in T2 glottic cancer did not influence prognosis to any major degree. They attributed this fact to the method of radiation treatment used⁷.

2. Dose Response

Controversy exists in the literature over the optimal dose-time-volume factors to be used in the radiotherapeutic management of T2 glottic cancer¹³⁻¹⁶. Harwood's results in terms of control by radiotherapy reported that there was a significant improvement in local control for an NSD (Nominal Standard Dose) of greater than 1650 ret versus less than 1650 ret; this improvement was seen in both subgroups of patients (mobility normal and mobility impaired)¹⁴. The Horiot et al study analyzed the failure patterns in the patients treated since 1959 and could not make a dose response curve. Since patients with bulkier T1 or T2 lesions received higher doses, there are different numbers of tumors at different dose levels. They expected that the incidence of poor voice and edema would sharply increase, thus negating the rationale behind choosing irradiation over surgery⁹. Karim et al noticed the dose response may be elicited with higher dosage, revealing the benefit of clinical radiotherapy and insisted that the principle of dose response should be applied for T2 glottic cancers by quality controlled radiotherapy in their study. Also, they reported that the high risk factors of these tumors, if recognized before initiating treatment, may be negated by quality-controlled radiotherapy^{15,16}.

The benefit of dose response in our study as compared to the result retrievable from the literature is inapparent (Table 4)¹⁶. A randomized study would be needed to prove this point specifically.

3. Surgical Salvage

Surgical salvages of T2 glottic cancer were too few to permit meaningful analysis. Local failures after radiation therapy for glottic carcinoma can be rescued by surgery; the success rate is high. Wang and associates retrospectively reported on 134 patients with local failure after treatment by radia-

tion therapy who underwent salvage surgery, 90 or 67% were NED. The salvage rate for T1 lesions was 79%. For T2 lesions, the salvage rate was 65%. Total laryngectomy was performed on 122 patients, partial laryngectomy (including cordectomy) in five, and cryosurgery in seven¹⁷. These data suggest that conservative surgical procedures for recurrences can be performed in a previously irradiated larynx without the risk of tissue breakdown if modern megavoltage techniques are used for this disease.

SUMMARY

For T2 lesions with normal cord mobility, without subglottic extension, radiotherapy as the treatment of choice provides great hope of local control. On the other hand, for the T2 lesions with impaired cord mobility or subglottic extension, the prognosis deteriorates, with approximately 45% of patients being controlled by radiation therapy. For such lesions, radiation therapy may be given initially as a curative procedure. If the tumor shows good response to radiation therapy with a return to normal cord mobility, radiation therapy may be successful. On the other hand, if the mobility remains impaired after radiation therapy, the patients should be re-evaluated in about 6 weeks with direct laryngoscopy and biopsy of suspicious lesions. If biopsy is positive for residual carcinoma, surgical salvage should be considered.

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국문초록

T2NO 병기 성문암의 방사선치료—예후인자 분석

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서 참 옥 · 김 귀 언 · 노 준 규

1978년 1월부터 1987년 12월 사이에 연세대학병원 치료방사선과에서 근치적 방사선치료를 받았던 44예의 T2NOMO 병기의 성문암 환자중 후향적 분석이 가능하였던 42예의 환자의 최소 추적기간은 3년 이었으며, 5년 추적조사 기간은 81%에서 가능하였다. 전체 환자(42예)의 5년 생존율 및 무병생존율은 각각 63.1% 및 53.3%이었다. 5년 무병생존율을 기초로한 성문의 운동성 장애와 성문암의 국소 침윤정도에 따른 예후인자의 분석에 있어서 성문의 운동성이 정상이고 성문 하부로의 침윤이 존재하지 않은 14예의 환자의 5년 무병생존율은 83.1%로 방사선 치료만으로도 성문의 운동성 장애가 있거나 성문 하부 침윤이 있었던 경우에 비하여 월등히 높은 치료 성적을 나타내어 T2NOMO 병기 내에도 방사선 치료에 다양한 반응을 보이는 아군(subgroup)이 존재함을 알 수 있었고 아울러 치료 실패 양상, 선량-반응 관계, 치료 실패환자의 수술요법 등에 관한 분석을 하여 향후 치료의 지침으로 삼고자하였다.