

A Study of Relationship Between PPC (Probability of Primary Clearance: a multivariate modelling system predicting tumor clearance proposed by RTOG) and Survival in the Patients with Carcinoma of the Nasopharynx Following Radiation Therapy

Kwan Ho Cho, M.D., Kyung Ran Park, M.D., Won Yong Oh, M.D., Mison Chun, M.D.
Chang Ok Suh, M.D., Gwi Eon Kim, M.D. and John J.K. Loh, M.D.

*Department of Radiation Oncology, Yonsei University
College of Medicine, Yonsei Cancer Center*

RTOG proposed a multivariate modelling system predicting the response of head and neck cancers to radiation therapy in 1984.

The aim of this study was to verify whether PPC (Probability of primary clearance calculated by a multivariate modelling system) had any correlation with the survival in the patients with carcinoma of the nasopharynx following radiation therapy.

Analysing 81 patients with carcinoma of the nasopharynx treated with radiotherapy between January 1, 1971 and December 31, 1983 at Yonsei University College of Medicine, Yonsei Cancer Center, the actuarial 5 year survival rate was 36% and median survival was 39 months. The survivals for Group 1 (27 who had more than 80% of PPC), Group 2 (20 who had between 71 and 80% of PPC), and Group 3 (29 who had less than 71% of PPC) were 66% (median survival months: more than 72), 27% (31), and 4% (12) respectively. There was a definite correlation between PPC and survival among the three groups.

Key words: Nasopharyngeal carcinoma, Radiation therapy, Probability of primary clearance, Survival.

INTRODUCTION

Through a lot of investigations, several parameters predicting the prognosis of the patients have been suggested in the treatment of malignant disease. Staging system might be a good example for them. Using the staging system, communication is possible with the other institutes, and also it has played an important role in choosing a treatment modality as well as predicting the prognosis of the patients following that therapy.

The indications for initial treatment of primary squamous cell carcinoma of the head and neck with radiation therapy have been debated for decades. Most physicians agree that small lesions (T₁ and T₂

according to AJC¹⁾ staging system) are best treated with radiation therapy as alternative surgical treatment results in physical deformity and/or organ dysfunction. Large lesions (T₃ and T₄) are usually treated with combinations of surgery and radiotherapy to give patients the best chance of local tumor control and subsequent cure.²⁻⁵⁾ In either case, the primary determinant of treatment historically has been tumor size.

This system for treatment selection is imperfect at best. The patient populations in those two groups are not homogenous. Not all patients with small tumors obtain a complete remission after irradiation.

tion, and many patients with large lesions are adequately treated with radiation therapy alone. The problem has been the lack of an accurate system which predicts the response of individual lesions in individual patients to treatment with radiation therapy.

In 1976, the Radiation Therapy Oncology Group opened a tumor registry for patients with carcinoma of the head and neck region. Their purpose was to establish a large data set on this group of patients. Among a total of 2,066 patients registered, 997 patients were eligible for their analysis after 1,069 being excluded in various reasons. Tumor factors (tumor size, tumor location, degree of differentiation, degree of infiltration, and presence or absence of metastatic cervical adenopathy) and host factors (nutritional status, alcoholism, heavy smoking, concurrent disease, general medical status, immune competency, age, and sex) were prospectively collected and recorded. The purpose of their study was to identify factors significantly associated with complete response of squamous cell carcinomas of the head and neck to irradiation from this data set, and from those factors construct a model that accurately identifies patients who have a high probability of complete primary clearance (PPC) from treatment with radiation therapy alone.

The pre-treatment factors were analyzed using the Cox multivariate logistic model to determine the significance of their association with complete primary tumor clearance after treatment with radiotherapy. The significant factors associated with the prediction of complete primary clearances were T-stage ($p = .001$), Karnofsky performance score ($p = .001$), site of primary ($p = .001$) and N-stage ($p = .007$). Using the factors that were found to be predictive of complete primary tumor clearance, the Cox logistic model was constructed and is given in Table 1. In order to solve the model for PPC (probability of primary clearance), the above mentioned four variables should be put into the model, and calculated.

The accuracy of the fitted model was tested by four variables. The ratios of the observed number of complete primary clearance to the predicted number of complete primary clearance (O/P) were calculated. To verify the accuracy of the predictive model, a second data set was analyzed. Consequently, it was reported that the model was quite predictive even in that second data set.⁶⁾

Even though primary tumor was completely disappeared following a given therapy, it had not been uncommonly experienced that the subsequent

metastases to regional lymph nodes and/or distant parenchymal organ or site were the primary cause of failure in the treatment of malignant disease.

Radiation therapy has been universally accepted as the treatment of choice for nasopharyngeal carcinomas. Although there was a minor differences by the investigators, approximately a half of the patients might be expected to be cured after treatment with radiation therapy. Despite the primary tumor was completely regressed after irradiation, the subsequent metastases to cervical lymph node(s) and/or distant organ or site(s), which affected, directly and definitely, the prognosis of the patients adversely, were not uncommonly observed.⁷⁻¹¹⁾

But, those investigators did not mention about the differences in survival with respect to the variation of PPC. If the variation of PPC doesn't make any differences in survival, what shall we find its significance from? The purpose of this study is to verify whether PPC has any correlations with the survival in the patients with carcinoma of the nasopharynx following radiation therapy, or not.

METHODS AND MATERIALS

Patient Selection and Characteristics

Between January 1, 1971 and December 31, 1983, eighty seven patients who were seen at Yonsei University College of Medicine, Yonsei Cancer Center, were found to have biopsy proven carcinoma of the nasopharynx. Among them, six patients were excluded from the evaluable patients, because three refused further work-up or treatment and the other 3 were initially treated for metastatic disease. The remaining 81 patients received definitive irradiation. Sixty two patients were male and 19 female. Their ages ranged from 15 to 71 with

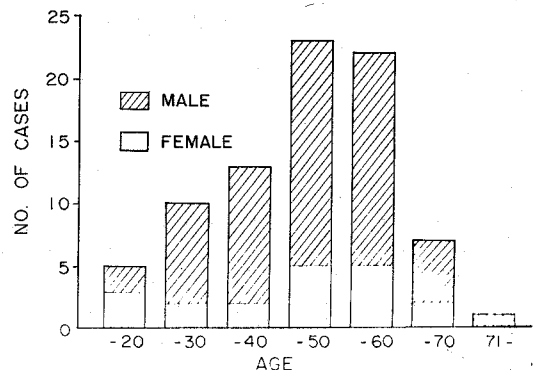


Fig. 1. Age and sex distribution.

an average of 45.0(Fig. 1).

Disease was staged prospectively based upon work-up including physical exam, indirect and direct nasopharyngoscopy, serum chemistries, base of skull tomograms and in recent years, CT scans. Bone scans and/or liver scans were not done routinely unless patients had signs or symptoms referable to these organs.

For purposes of this report, tumors staged prior to 1983 were restaged retrospectively by the 1983 criteria of the American Joint Committee for Cancer. After 1983, tumors were staged prospectively by the same system. By these standards, none were in Stage I disease, 4, Stage II, 12, Stage III, and 63, Stage IV (Table 2). Two patients could not be staged because of lack of sufficient information. Distribution of patients by histologic findings is shown in Table 3.

Technique and Dose of Radiotherapy

The radiation technique including dosage

Table 1. Multivariate Model for Predicting Tumor Clearance with Radiation Therapy Alone

$\ln (P/1-P) = 2.100-0.960 (T-2.072)-0.245 (N-0.622) + 0.855 (S-1.854) + 0.716 (K-1.613)$	
P	Probability of Primary Clearance
T	T-stage (1, 2, 3, 4)
N	N-stage (0, 1, 2, 3)
S	Site (1 = oral cavity 2 = oropharynx, hypopharynx, supraglottic & glottic larynx 3 = nasopharynx)
K	Karnofsky Performance Score (0 = less than 70%, 1 = 70-80%, 2 = 90-100%)

Table 2. Stage (AJC)

Stage	No. of cases (%)
Stage I	0 (-)
Stage II	4 (4.9)
Stage III	12 (14.8)
Stage IV (loco-regionally advanced)	63 (77.8)
Unknown	2 (2.5)
No. of cases	81 (100.0)

schedule has been relatively constant during the study period. All patients received megavoltage irradiation from the tele-Cobalt 60 apparatus combined with or without 8- or 12-MeV electron beam generated from linear accelerator.

Parallel opposed lateral fields were used to encompass the primary nasopharyngeal disease, the base of skull and at least the first eschelon of draining nodes. A supplemental anterior port was used only for those patients having anterior extension of disease into the nasal cavity. An anterior single port was routinely used for the entire lower neck, and boost irradiation was given, if necessary. All fields were treated every day, 180-200 cGy per fraction, and five times a week.

Seventy five of the 81 patients received at least 6,000 cGy and 15 received more than 7,000 cGy to the nasopharynx. Sixty of the 67 patients who had clinically palpable lymph nodes, received at least 6,000 cGy and 9 of the 14 patients who had sub-clinical disease were irradiated at least 5,000 cGy (Table 4 and 5).

Table 3. Pathology

Pathology	No. of case (%)
Squamous	39 (48.1)
Lymphoepithelioma	42*(51.9)
No. of cases	81

*Included undifferentiated cell carcinoma: 12 cases

Table 4. Dose Delivered to Primary Site

Dose (cGy)	No. of cases (%)
More than 6,999	15 (18.5)
6,000 — 6,999	60 (74.1)
5,000 — 5,999	3 (3.7)
Less than 5,000	3 (3.7)
No. of cases	81

Table 5. Dose Delivered to Neck Node Area

Dose	No. of cases		No. of cases (%)
	Clinically Positive	Clinically Negative	
More than 6,999	25	0	25 (30)
6,000 — 6,999	35	3	38 (46)
5,000 — 5,999	4	6	10 (12)
Less than 5,000	3	5	8 (9)
No. of cases	67	14	81

Method of Analysis

In order to obtain the PPC of the individual patients, four individual variables were put into the multivariate model for predicting tumor clearance. It was calculated in percentage. In order to have even distributions, the patients were divided into three groups(Fig. 2). Group 1 included 27 patients who had had more than 80% of PPC, Group 2 included 20 who had had between 71 and 80% of PPC, and

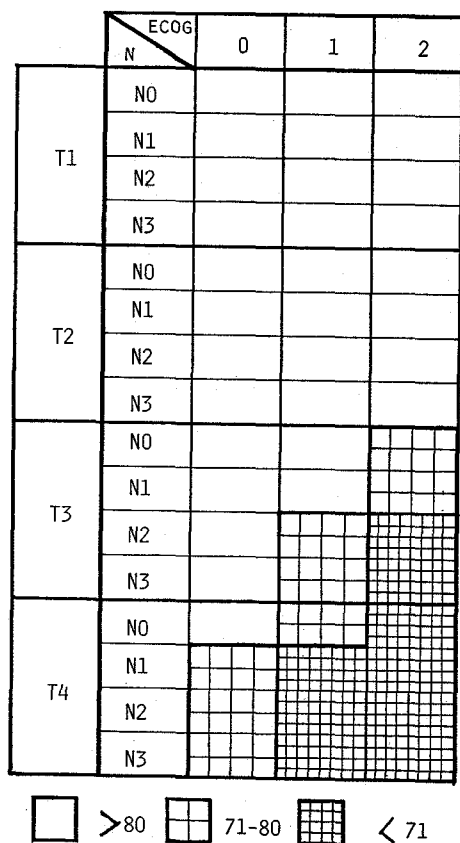


Fig. 2. Diagram of PPC(%) in nasopharyngeal Cancer.

Table 6. PPC

PPC (%)	No. of cases (%)
More than 80	27 (33.3)
71 — 80	20 (24.7)
Less than 71	29 (35.8)
Unknown	5 (6.2)
No. of cases	81

Group 3 included 29 who had had less than 71% of PPC(Table 6). In five cases, PPC couldn't be calculated because of inadequate informations.

Survival rates have been calculated according to the actuarial method described by the American Joint Committee. Analysis was done as of 7/30/85. Most of follow-ups were made with physical examination. In some cases, follow-up informations were obtained either from a census registry of the administrative office or telephone inquiry. Sixty eight of the 81 patients (84%) could be able to be followed-up in this way.

RESULTS

The actuarial 5 year survival rate for all patients studied was 36% (median survival months: 39); 63%(75) for Stage I-III, and 22%(24) for Stage IV.

According to the PPC, actuarial 5 year survival rates were 66%(median survival months: more than 72), 27%(31), and 4%(12) for Group 1, 2, and 3 respectively. There was a definite correlation between PPC and survival among the three groups (Fig. 3 and Table 7).

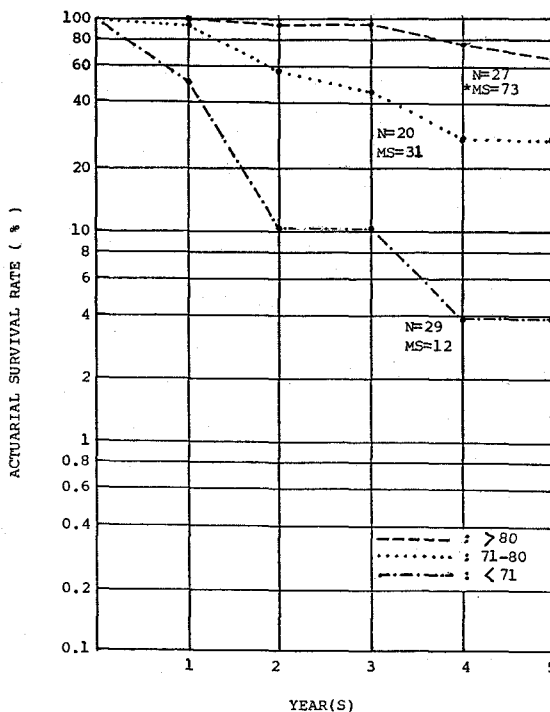


Fig. 3. Survival vs. PPC(%) in nasopharyngeal cancer plotted on semi-log graph.

*MS= Median Survival Months

Table 7. PPC vs. Actuarial Survival Rates (%)

PPC (%)	5YSR (%)	*MS	**N	+ P
More than 80	66.4	73	27	
71 — 80	27.2	31	20	0.001
Less than 71	3.9	12	29	0.005

*MS = median survival months

**N = number of cases

+ P = probability

CONCLUSION

RTOG proposed a multivariate modelling system predicting the response of squamous cell carcinoma of the head and neck to radiation therapy in 1984. PPC calculated by the multivariate model and survival had a definite correlation in the patients with carcinoma of the nasopharynx following radiation therapy.

If the model is applied to the individual patients at the time of initial presentation, it would be helpful for predicting the prognosis of the patients because the system has several unique determining prognostic variables. In addition, it might be possible to communicate with the other institutes using the PPC beside staging system.

REFERENCES

1. American Joint Committee on Cancer. Manual for staging of cancer. 2nd ed, Philadelphia, JB Lippincott, 1983
2. Hamberger AD, Fletcher GH, et al: Advanced squamous cell carcinoma of the oral cavity and oropharynx treated with irradiation and surgery. *Radiology* 119:433-438, 1976
3. Harwood AR, Hawkins NV, et al: Radiotherapy of early glottic cancer. *Int J Radiat Oncol Biol Phys* 5:1971-1976, 1979
4. Wang CC: Megavoltage radiation therapy for supraglottic carcinoma, results of treatment. *Radiology* 109:183-186, 1973
5. Kazem I, Van Den Brook P, et al: Planned pre-operative radiation therapy for advanced laryngeal carcinoma. *Int J Radiat Oncol Biol Phys* 8:1533-1537, 1982
6. Griffin TW, Pajak TF, et al: Predicting the response of head and neck cancers to radiation therapy with a multivariate modelling system: an analysis of the RTOG head and neck registry. *Int J Radiat Oncol Biol Phys* 10:481-487, 1984
7. Cho KH, Kim SK, et al: Result of definitive irradiation for regional stage IV carcinoma of the nasopharynx: an analysis of the patterns of failure. To be published.
8. Hoppe RT, Goffinet DR, et al: Carcinoma of the nasopharynx, eighteen years' experience with megavoltage radiation therapy. *Cancer* 37:2605-2612, 1976
9. Mesic JB, Fletcher GH, et al: Megavoltage irradiation of epithelial tumor of the nasopharynx. *Int J Radiat Oncol Biol Phys* 7:447-453, 1981
10. Bedwinek JM, Perez CA, Keys DJ: Analysis of failures after definitive irradiation for epidermoid carcinoma of the nasopharynx. *Cancer* 45:2725-2729, 1980
11. Cooper JS, Rowe JD, Newall J: Regional stage IV carcinoma of the nasopharynx treated by aggressive radiotherapy. *Int J Radiat Oncol Biol Phys* 9:1737-1745, 1983

= 국문초록 =

비인강암의 방사선치료 : RTOG 에서 제시한 PPC와 생존율에 대한 고찰

연세대학교 의과대학 연세암센터, 치료방사선과

조관호 · 박경란 · 오원웅 · 전미선 · 서창욱 · 김귀언 · 노준규

1984년 RTOG 에서 두경부 편평세포암의 방사선치료시, 원발병소의 완전관해 가능성을 예측할 수 있는 Multivariate Modelling System 을 제시하였다.

저자들은 1971년 1월부터 1983년 12월까지 조직병리학적으로 확진된 비인강암으로 연세대학교 의과대학 연세암센터, 치료방사선과에 내원하여 근치적 방사선 치료를 받은 81예를 대상으로, 그들이 제시한 system 에 의해 계산된 PPC(Probability of Primary Clearance : 원발병소 완전관해 가능성)와 생존율과의 관계를 후향적으로 분석 고찰하였다.

全例를 대상으로 한 5년 생존율은 36%, 중앙생존기간은 39개월이었다. 편의상, PPC 에 따라 3군으로 구분하였고, 각군에 따른 생존율은 Group 1 (PPC 가 81%이상인 27예)은 66%(중앙생존기간: 72개월이상), Group 2(PPC 가 71~80%의 20예)는 27%(31개월) 및 Group 3(PPC 가 70%이하의 29예)의 4%(12개월)순이었다. 그리고 각 Group 간의 PPC 와 생존율은 통계학적으로 유의한 차이를 보였다.