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Treatment results and prognostic factors of patients undergoing postoperative radiotherapy for laryngeal squamous cell carcinoma

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Abstract

Postoperative radiotherapy (PRT) is widely advocated for patients with squamous cell carcinomas of the head and neck that are considered to be at high risk of recurrence after surgical resection. The aims of this study were to evaluate the treatment outcomes of PRT for patients with laryngeal carcinoma and to identify the value of several prognostic factors. We reviewed the records of 256 patients treated for laryngeal squamous cell carcinoma between January 1993 and December 2005. Disease-free survival (DFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Log-rank test was employed to identify significant prognostic factors for DFS and OS. The Cox proportional hazards model was applied to identify covariates significantly associated with the aforementioned endpoints. Our results showed the 3-, 5-, and 10-year DFS for all patients were 69.9%, 59.5%, and 34.9%, respectively. The 3-, 5-, and 10-year OS rates were 80.8%, 68.6%, and 38.8%, respectively. Significant prognostic factors for both DFS and OS on univariate analysis were grade, primary site, T stage, N stage, overall stage, lymph node metastasis, overall treatment times of radiation, the interval between surgery and radiotherapy, and radiotherapy equipment. Favorable prognostic factors for both DFS and OS on multivariate analysis were lower overall stage, no cervical lymph node metastasis, and using ^{60}Co as radiotherapy equipment. In conclusion, our data suggest that lower overall stage, no cervical lymph node metastasis, and using ^{60}Co as radiotherapy equipment are favorable prognostic factors for DFS and OS and that reducing the overall treatment times of radiation to 6 weeks or less and the interval between surgery and radiotherapy to less than 3 weeks are simple measures to remarkably improve treatment outcome.

Key words Surgery, postoperative radiotherapy, squamous cell carcinoma, larynx, prognosis factors, survival

Head-and-neck cancer is the sixth most prevalent cancer in the world, with an incidence of 700 000 cases per annum[1]. Of all head-and-neck tumors, 20% originate in the larynx. Postoperative radiotherapy (PRT) is widely advocated for patients with head-and-neck squamous cell carcinomas considered to be at high risk of recurrence after surgical resection. The most frequently mentioned risk factors for locoregional recurrences and survival are the staging according to the TNM classification[2–8], quality of surgical resection[2,3,9–12], perineural growth[13–15], the size and number of positive neck nodes[9,16], and the presence of extranodal spread[9,11,13,17] as well as, in some studies, age and gender[8]. Besides prognostic factors directly related to the tumor or the surgical specimen, treatment-related variables may also account for differences in clinical outcome, including the total dose of radiation, the duration of the interval between surgery and radiotherapy and the overall treatment time of radiation. In a prospective randomized study, conventionally fractionated radiot herapy (63 Gy in 7 weeks) was

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compared with accelerated radiotherapy (63 Gy in 5 weeks) in the postoperative setting. The rationale for accelerated fractionation is that a reduction of the overall treatment time reduces the risk of tumor cell repopulation during treatment and therefore improves the probability of locoregional tumor control. In this study, a trend toward higher locoregional control rates was found when PRT was administered in 5 instead of 7 weeks. Furthermore, a prolonged interval between surgery and radiotherapy in the 7-week schedule was associated with a significant reduction in locoregional control [18]. In another prospective randomized study conducted at the M. D. Anderson Cancer Center, a significant higher locoregional recurrence rate was found among patients who received a dose of ≤54 Gy than among those who received a dose of ≥57.6 Gy [17].

In the aforementioned prospective studies, although all these patients had squamous cell carcinoma, the clinical behavior and the additional effect of treatment modifications may differ between various tumor sites [9,12,17,19]. For this reason, the analysis of prognostic factors and verification of the effects of treatment modification in various subsites within the head and neck may provide important additional information. Thus, the current study was undertaken to evaluate the results of PRT in the subset of patients with squamous cell carcinoma arising in the larynx.

Materials and Methods

Patient characteristics

Between January 1993 and December 2005, 256 patients with previously untreated squamous cell cancer of the larynx were treated with PRT on Cobalt-60 (^{60}Co) units or a 6-MV linear accelerator at the Sun Yat-sen University Cancer Center in Guangdong, China. Chemotherapy was not used in this group. There were 252 male and 4 female patients. The median age at diagnosis was 60 (range, 23–85) years. Follow-up examination was started after treatment; the last follow-up was March 29th, 2009, with a median follow-up time of 86.5 months (range, 2–203 months). Twenty-five (10.1%) patients were lost from the follow-up prior to 2 years. Patient characteristics have been summarized in Table 1. Patients were re-staged according to the guidelines of the 2002 Union for International Cancer Control (UICC) on Cancer staging system.

Surgery

Of the 256 patients with laryngeal cancer, 63 (24.7%) were treated with total laryngectomy, 187 (73.0%) with partial laryngectomy including 46 patients (24.6%) with chordectomy and 6 (2.3%) did not receive surgery for the laryngeal cancers but had unilateral or bilateral neck node dissection. All patients underwent a major surgical intervention (i.e., patients irradiated after excisional biopsies were excluded). Unilateral or bilateral neck node dissection was performed on 140 (54.7%) patients. Surgery was performed in all cases in our center.

Radiotherapy

The indications for PRT in our hospital during the study included clinically or microscopically positive surgical margins, pathologically positive neck nodes and advanced primary laryngeal cancer (stages T3 and T4). Only patients in good general condition with no distant metastases were considered for PRT.

The interval between surgery and radiotherapy was ≤2 weeks in 73 patients (28.5%), 2 to 4 weeks in 122 patients (47.7%), 4 to 6 weeks in 39 patients (15.2%), and more than 6 weeks in 22 patients (8.6%). Radiotherapy was delivered employing ^{60}Co units or 6-MV linear accelerator. Total radiation dose in the area of clinical target volume ranged from 10 to 82 Gy, with a median value of 60 Gy. Low doses (<50 Gy) were given to patients whose clinical condition demanded premature termination of treatment (e.g., local progression during PRT, deteriorating performance status, and intercurrent disease) or to those who refused completion of treatment. High doses (>70 Gy) were given to patients with a clinically palpable mass remaining after the surgery or to patients in need to increase the total dose because of a long duration due to treatment gaps.

Statistical analyses

Disease-free survival (DFS) and overall survival (OS) were calculated from the day of surgery. In the univariate analysis, DFS and OS were estimated with the Kaplan-Meier method and the statistical significance of differences between curves was tested by using the log-rank test. A multivariate analysis using the Cox proportional hazards model was performed to identify covariates that were significantly associated with the aforementioned endpoints. The statistical analysis was performed using the SPSS/PC 11.0 software package. A value of $P < 0.05$ was considered as significantly different.

Results

Disease-free survival

The 3-, 5- and 10-year DFS for patients was 69.9%, 59.5% and 34.9%, respectively (Figure 1). Significant prognostic factors on univariate analysis showed that grade, primary site, T stage, N stage, overall stage, lymph node metastasis, overall treatment times of radiation, the interval between surgery and radiotherapy, and radiotherapy equipment were significant prognostic factors (Table 1). Multivariate analysis showed that no cervical lymph node metastasis, lower overall stage, and using ^{60}Co as radiotherapy equipment were favorable prognostic factors for DFS (Table 2).

Overall survival

Overall 3-, 5- and 10-year survival rates for the entire group were 80.8%, 68.6%, and 38.8%, respectively (Figure 1). The 5-year cumulative overall survival rates were significantly different among patients with different stage diseases grouped according to pathologic UICC stage ($P < 0.001$), as shown in Table 1. Univariate analysis indicated that grade, primary site, T stage, N stage, overall stage, lymph node metastasis,

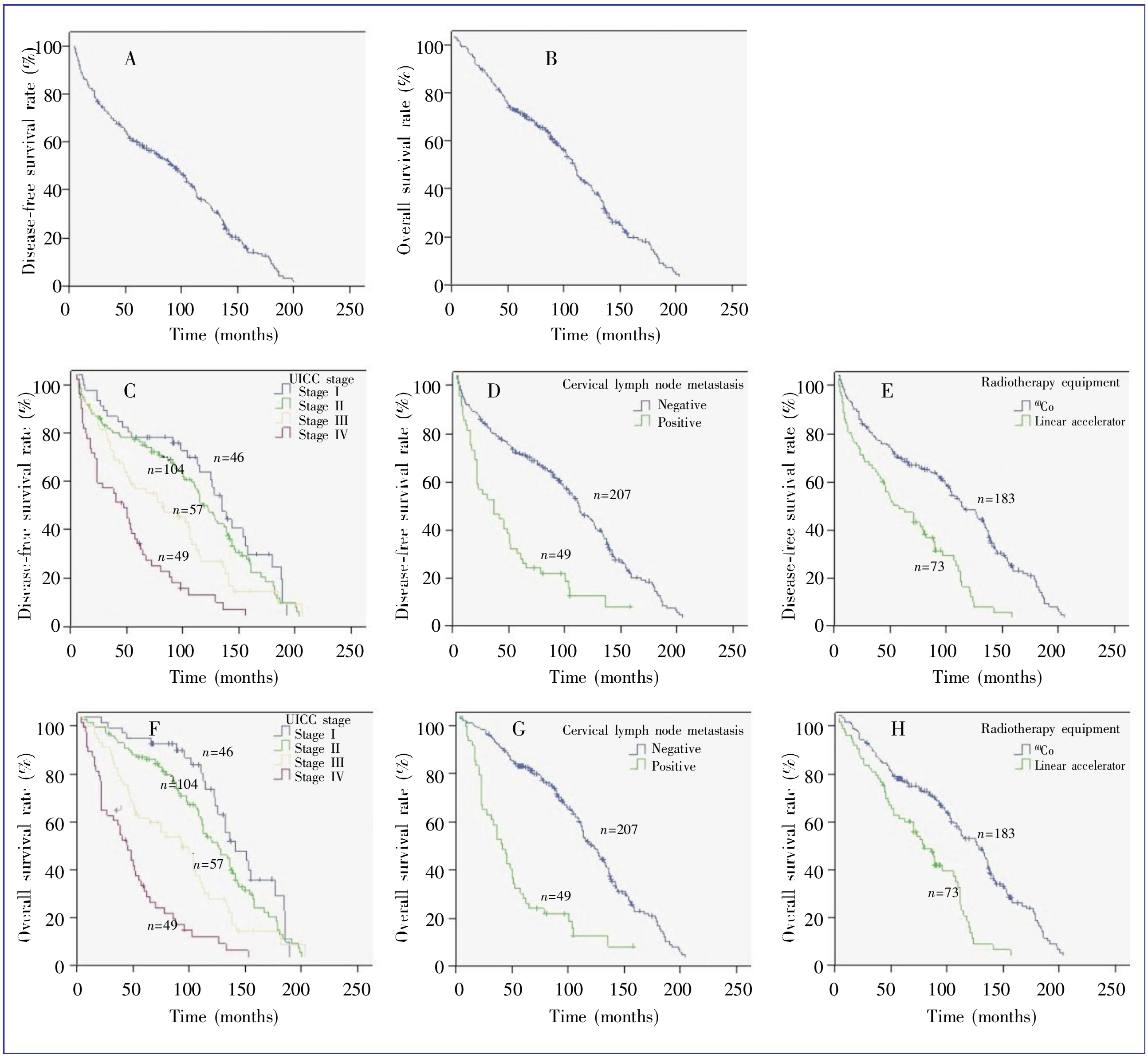

Figure 1. **Survival curves of various groups of patients.** A, disease-free survival (DFS) in all patients; B, overall survival (OS) in all patients; C, DFS in patients with different UICC stage diseases; D, DFS in patients with or without cervical lymph node metastasis; E, DFS in patients treated with different radiotherapy equipments; F, OS in patients with different UICC stage diseases; G, OS in patients with or without cervical lymph node metastasis; H, OS in patients treated with different radiotherapy equipments.

Table 1. Univariate analysis of prognostic factors for disease-free survival (DFS) and overall survival (OS)

Prognostic factor	No. of patients	5-year DFS (%)	χ^2	P [a]	5-year OS (%)	χ^2	P [a]
Gender			0.004	0.947		0.05	0.823
Male	252	58.9			68.1		
Female	4	100.0			100.0		
Age (years)[b]			0.180	0.671		0.002	0.963
≤60	129	61.1			68.9		
>60	127	57.9			68.3		
Smoking index[c]			0.745	0.388		1.003	0.317
<400	66	57.1			68.1		
≥400	190	60.4			68.8		
Alcohol consumption			0.144	0.705		0.730	0.393
No	155	59.0			70.2		
Yes	101	60.3			66.2		
Grade			17.745	**<0.001**		9.304	**0.010**
Well differentiation	120	71.5			79.0		
Moderate differentiation	104	50.0			62.5		
Poor differentiation	32	44.7			49.3		
Primary site			40.091	**<0.001**		56.350	**<0.001**
Glottis	173	69.1			79.6		
Supraglottis	57	36.8			42.1		
Subglottis	6	66.7			83.3		
Transglottis	19	36.8			42.1		
Blood type			1.554	0.670		1.457	0.692
A	80	62.5			70.0		
B	63	64.5			69.5		
AB	23	65.2			73.9		
O	90	52.1			65.4		
T stage			31.082	**<0.001**		50.212	**<0.001**
T1	46	73.9			91.3		
T2	120	68.1			77.4		
T3	57	45.5			52.5		
T4	33	32.1			32.0		
N stage			59.194	**<0.001**		105.232	**<0.001**
N0	207	67.9			79.1		
N1	24	37.5			37.5		
N2	22	13.6			13.6		
N3	3	0.0			0		
UICC stage			49.756	**<0.001**		87.327	**<0.001**
I	46	73.9			91.3		
II	104	71.9			83.6		
III	57	52.6			57.8		
IV	49	27.6			27.5		
Cervical lymph node metastasis			37.678	**<0.001**		67.413	**<0.001**
No	207	67.9			79.1		
Yes	49	24.5			24.5		
OTTRT[d]			3.919	**0.048**		4.212	**0.040**
0–42 times	148	64.1			73.5		
>42 times	108	54.2			61.9		
T_{SPRT}[e]			13.352	**<0.001**		12.129	**<0.001**
0–19 days	73	69.0			76.8		
>19 days	22	49.7			60.1		
Total radiation dose (Gy)			3.686	0.055		3.214	0.073
<60	112	65.0			74.0		
≥60	144	55.2			64.4		
Radiotherapy equipment			32.021	**<0.001**		28.868	**<0.001**
^{60}Co	183	65.3			73.1		
6 MV linear accelerator	73	44.9			57.3		
Margin			0.399	0.527		1.084	0.298
Negative	145	60.5			69.5		
Positive	111	58.2			67.4		
Extracapsular spread			13.352	**<0.001**		12.129	**<0.001**
No	35	69.0			76.8		
Yes	14	49.7			60.1		
Type of surgery			19.567	**<0.001**		23.230	**<0.001**
Only neck dissection	6	33.3			33.3		
Partial laryngectomy	187	67.8			78.0		
Total laryngectomy	63	37.5			43.9		

[a] Bold *P* values are significant by the log-rank test.
[b] Patients were divided into two groups according to the median age.
[c] Smoking index is defined as the number of cigarettes used per day × the total smoking time (years).
[d] Patients were divided into two groups according to the median value of overall treatment times of radiation (OTTRT).
[e] Patients were divided into two groups according to the median values of the interval between surgery and radiotherapy (T_{SPRT}).

overall treatment times of radiation, the interval between surgery and radiotherapy and radiotherapy equipment were the risk factors (Table 1). Multivariate analysis showed that lymph node metastasis, overall stage and radiotherapy equipment were independent prognostic factors (Table 2).

Discussion

Prognostic factor significance was evaluated among patients with squamous cell carcinoma of the larynx after treatment with primary surgery and PRT. None of these patients received other forms of adjuvant systemic treatment. Results showed the 5-year OS of patients was significantly related to the UICC total stage, indicating that initial classification (T stage, N stage and total stage) are statistically related to the risk of survival; these results are similar to those previously reported[2-8,20-23]. In our study, the univariate statistical analysis also indicated the presence of tumor site (supraglottis or transglottis) correlates with poor prognosis.

It has been reported that the number, site and volume of metastatic lymph nodes negatively influence the prognosis of laryngeal carcinoma[24,25] and that a poor degree of tumor differentiation negatively influences prognosis[26,27]. These results were substantially confirmed by our study, in which univariate analysis showed that a poor degree of differentiation ($P < 0.001$) or the presence of metastatic lymph nodes ($P < 0.001$) carry a negative prognostic value. The relationship between nodal involvement and local control has been examined in many patient series. The results of van den Bogaert *et al.*[28] (local control 70% at 5 years in patients without positive nodes vs. 49% in patients with clinically positive node, $P < 0.05$) and Wall *et al.*[29] (79% vs. 57%, $P < 0.05$) are comparable. In addition, three large multicenter studies on PRT have reported similar recurrence rates[30-32]. The general conclusion of these studies is that the status of the cervical lymph nodes seems to be the most important tumor-related prognostic factor for head-and-neck cancer patients. Not only the incidence of local recurrence, but also the risk of distant metastases increases as the tumor burden in the neck increases[33,34].

In some studies, the time interval between surgery and irradiation has been recognized as an important end point[2,12,17,18,35,36]. In the present study, univariate analysis showed the interval between surgery and radiotherapy is a significant prognostic factor. Postoperative irradiation of the primary tumor site and lymph nodes has been shown to decrease the risk of locoregional relapse[37-39]. After surgical removal, the percentage of residual cancer cells is primarily related to the quality of surgical resection (margins' pathologic state) as well as the duration of the delay in regard to the potential doubling time of tumor cells[40]. The potential doubling time of solid tumors can be brief, particularly in some types of head-and-neck cancer[41]. Therefore, it seemed logical to consider that remnant cancer cells could proliferate in the case of delayed radiotherapy. Thus, radiotherapy should begin as soon as healing is complete; it can often be started within 3 to 4 weeks of surgery. If radiotherapy is delayed until gross recurrence has occurred, the chance for successful salvage by radiotherapy is only 5% to 10%[42-44]. If healing is not complete by 6 weeks, institutional data indicate radiotherapy can often be safely initiated and approximately 66% of patients will heal spontaneously during or after the course of radiotherapy[12,45].

In the present study, a shorter overall treatment time of radiation was associated with higher rates for DFS and OS. Two major factors are responsible for heterogeneity of overall treatment time in radiotherapy:

Table 2. Multivariate analysis of DFS and OS with proportional hazard Cox model

Variable	DFS			OS		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI[a]	*P*
Primary site	1.023	0.974–1.074	0.362	1.022	0.974–1.073	0.368
Grade	1.175	0.961–1.438	0.116	1.106	0.894–1.368	0.353
Cervical lymph node metastasis	1.680	1.101–2.564	**0.016**	2.180	1.422–3.341	**<0.001**
UICC stage	1.327	1.106–1.591	**0.002**	1.566	1.291–1.901	**<0.001**
OTTRT	1.009	0.744–1.370	0.952	1.031	0.750–1.416	0.852
T_{SPRT}	1.119	0.817–1.533	0.485	1.008	0.728–1.396	0.962
Radiotherapy equipment	2.090	1.489–2.933	**<0.001**	2.091	1.467–2.980	**<0.001**

CI, confidence interval.

diversity in fractionation and unplanned radiation treatment interruption. Unlike in the clinical trials on time effect in PRT [18,46], in which altered fractionation was responsible for the diversity in overall treatment time, the range of overall treatment time in the present series was mostly the result of unplanned treatment gaps. Langendijk *et al.* [47] observed the locoregional control worsened approximately 9% with each additional week in prolongation of overall treatment. In addition, Suwinski *et al.*[48] noticed prolongation of overall treatment by 10 days was related to a 10% to 20% average decrease in the 5-year relapse-free survival and a 10% decrease in tumor control probability. Their results are identical to those reported in the first large review of retrospective data from the radiotherapy of head-and-neck cancer[49]. Moreover, their results support the findings reported by other investigators in prospective randomized studies in a postoperative setting[18,46,50]. Suwinski *et al.*[48] suggests a one-day extension in overall treatment time may be compensated for by a dose of approximately 1 Gy, providing, however, the delivery of an extra dose would not extend the overall treatment time. However, as no extra dose can be given without additional toxicity, they postulate preventing unplanned treatment gaps and not compensating for them by dose escalation should be implemented whenever possible.

In the present study, both univariate and multivariate analyses showed that different radiotherapy equipment is a significant prognostic factor. The main reason is due to a dose build-up effect caused by high energy X-rays, which will leave from the front of the vocal cords and neck to a low dose area. Frequently, early-stage laryngeal cancer generates from the front of the vocal cords. Alternatively, advanced laryngeal cancer is always spread to the front of neck (such as skin and thyroid cartilage). After surgical removal, many residual cancer cells remain in front of the vocal cords and neck if the quality of surgical resection (margins' pathologic state) is poor. Izuno *et al.*[51] observed the local control rate was significant higher in patients treated with ^{60}Co or 4 MV X-ray than in those treated with 8 MV X-ray or 10 MV X-ray. In addition, Shimizu *et al.*[52] reported the dose to the anterior commissure was reduced 12% with 6 MV X-ray and 18% with 10 MV X-ray compared with ^{60}Co. However, several investigators have observed that different treatment energies (such as ^{60}Co and 2 MV, 4 MV, 6 MV, and 10 MV X-ray) in the treatment of early-stage vocal cord cancer had almost similar local control rates [53-55]. Possible explanations for the discrepancies may be the development of modern radiotherapy techniques and clinical experience such as the use of bolus, multi-field irradiation techniques and hyperfractionation techniques. Notably, the aforementioned research investigated early-stage glottic cancer. In our study, we found the percentage of late stage (UICC stages III and IV) patients treated with linear accelerators is greater than the percentage of patients treated with ^{60}Co (51.9% vs. 38.8%, P = 0.038), which may be the main reason that using ^{60}Co as radiotherapy equipment exhibits favorable prognostic factors for DFS and OS in our research. Further studies are warranted to determine whether the application of different radiotherapy equipment leads to different outcome for patients receiving postoperative irradiation for advanced laryngeal cancer.

The major criticism of retrospective studies is that the data collected were not originally designed for a research application. Therefore, some factors responsible for the ultimate treatment outcome might be omitted in the analysis, contributing to bias. Such censure correctly refers to the present study, in which the data were heterogeneous and of lesser quality according to present standards. A disturbing feature of the data set is that 25 (10.1%) patients were lost from follow-up prior to 2 years after treatment. Considering these factors, one should realize conclusions from this study should be validated in future projects.

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