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PRIMARY IRRADIATION, SURGERY OR COMBINED THERAPY IN SQUAMOUS CELL CARCINOMA OF THE LARYNX

A comparison of treatment results from two centers

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Abstract

We compared two groups of patients with squamous cell carcinoma of the larynx. Group 1 consisted of 483 patients treated from 1958 through 1978. Primary surgery was selected in 41%, pre- or postoperative radiation therapy in 16% and primary radiation therapy in 43%. Group 2 consisted of 247 patients treated from 1978 through 1983. Primary surgery was selected in only 1.6%, pre- or postoperative radiation therapy in 23%, and primary radiation therapy, with surgery in reserve for residual or recurrent carcinoma, in 76%. Although the results were comparable for patients with early stage tumors in the two groups, significantly higher local-regional tumor control rates and corrected survival rates were recorded for patients with advanced tumors in group 2. More patients survived with a cancer-free functional larynx, the surgical salvage rates were higher, the complication rates and the death rates lower in group 2 compared to group 1.

Key words: Laryngeal carcinoma, treatment results, comparison.

Uncertainty still exists in many institutions about the role of radiation therapy in the primary treatment of squamous cell carcinoma of the larynx. Patients seeking advice may be presented with conflicting views. Some surgeons recommend primary surgery on principle and primary radiation therapy only in patients who present with medical contraindications to surgery or as a postoperative adjuvant in patients with advanced neck node metastases. (1) In other institutions, primary radiation therapy is recommended for the majority of patients, with surgery reserved for patients who fail to be controlled with radiation therapy or as planned pre- or postoperative adjuvant therapy. (2).

In order to throw some light on this subject, we reviewed the results of two institutions which have different treatment policies on this subject.

Material and Methods

The material is summarized in Table 1. Two institutions contributed the patients to the study; The University of Wisconsin Hospitals, Madison (group 1) and the Norwegian Radium Hospital, Oslo (group 2). The hospital charts of 821 patients were reviewed and represented the total number of cases referred over a period of 26 years from a population base of some 4 million for each institution. The staging was performed according to the UICC 1978 staging system, retrospectively based on the information recorded in the hospital charts in group 1, prospectively after the diagnostic work-up in group 2. The age and sex of the patients and the anatomical location of the primary tumor did not differ significantly. A group of patients recorded as having transglottic tumors in group 1 had a clinical picture and prognosis similar to those with advanced supraglottic tumors and were included as such in the final analysis. A small group of patients with subglottic primary tumors (1% of the total) also had a similar prognosis and were included in the same group. The

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Table 1
Carcinoma of the larynx

Material	Group 1 U. Wisconsin Hosp.	Group 2 Radium Hosp.	Total
Years of admission	1/1-1958 to 1/1-1979	1/1-1978 to 1/1-1984	
Number of patients	566	255	821
Primary treatment	509	255	764
Secondary treatment (Recurrence after prim. treatment elsewhere)	57	0	57
Age on admission			
< 50	78 (14%)	20 (8%)	
50-70	378 (67%)	168 (66%)	
> 70	110 (19%)	67 (26%)	
Sex			
Men	511 (90%)	227 (89%)	
Women	55 (10%)	28 (11%)	
Localization			
Supraglottic	223 (39%)	97 (38%)	
Glottic	271 (48%)	155 (61%)	
Subglottic	5 (1%)	3 (1%)	
Transglottic	60 (11%)	0	
Unknown	7 (1%)	0	
Histology			
Squamous cell carcinoma	549 (97%)	254 (99.6%)	
Verrucous sq. cell ca.	2	1	
Carcinoma in situ	6	0	
Adenocarcinoma	4	0	
Unknown or uncertain	5	0	
Clinical stage (UICC 1978)			
T1N0	139 (25%)	75 (29%)	
T2N0	99 (17%)	64 (25%)	
T3N0	75 (13%)	34 (13%)	
T4N0	87 (15%)	31 (21%)	
N1	79 (14%)	30 (12%)	
N2N3	70 (12%)	15 (6%)	
M1	17 (3%)	6 (3%)	

clinical stages were also similar in the two groups, except for N2N3 tumors, which were twice as common in group 1 as in group 2 (12% vs. 6%). In group 1, 57 patients who were referred for evaluation of recurrent tumors after having received primary treatment elsewhere, were deleted (Table 2). Also deleted were those in whom the diagnosis of infiltrating squamous cell carcinoma could not be con-

firmed, those with distant metastases on admission, and those who received no treatment. All other patients were included without selection, also those who did not complete their prescribed treatments. The remaining 483 patients in group 1 and 247 patients in group 2 were subjected to final analysis.

Selection of primary treatment was made by the laryngologist after complete staging work-up, and the patients were referred for either primary radiation therapy or surgery (Table 3). Primary surgery was performed in 41%

Table 2
Deletions from the total patient material

	Group 1 U. Wisconsin Hosp.	Group 2 Radium Hosp.
Primary treatment elsewhere	57	0
Histology of infiltrating squamous cell carcinoma not confirmed	12	0
Distant metastases on admission	8	6
No treatment given	6	2
Total	83	8
Total patients remaining for final analysis	483	247

Table 3
Selection of primary treatment for squamous cell carcinoma of the larynx

	Group 1 U. Wisconsin Hosp.	Group 2 Radium Hosp.
Surgery alone	197 41%	4 1.6%
Radiotherapy alone	209 43%	187 76%
Preoperative radiotherapy	37 8%	36 15%
Postoperative radiotherapy	40 8%	20 8%
Total	483 100%	247 100%

Table 4
Radiation dosage in treatment of cancer of the larynx

Stage Location	U. Wisconsin Hosp. Dose (CRE)		No. of patients	Radium Hosp. Dose (CRE)		No. of patients
	Median	(Range)		Median	(Range)	
T1N0						
Glottis	1860	(1600-2030)	64	1910	(1560-1950)	63
Supraglottis	1870	(1620-1940)	6	1920	(1670-1950)	11
T2N0						
Glottis	1810	(1080-1960)	28	1925	(1760-1950)	50
Supraglottis	1930	(1820-2100)	16	1930	(1880-1950)	13
T3N0						
Glottis	1700	(920-1760)	11	1925	(755-1950)	16
Supraglottis	2000	(1920-2120)	10	1920	(1905-1940)	5
T4N0						
Glottis	1860	(1460-1940)	5	1940	(1555-1940)	3
Supraglottis	1840	(1280-2020)	17	1820	(1550-1940)	7
T1-4N1						
Glottis	1880	(1600-1900)	3	1890	(1555-1930)	3
Supraglottis	1780	(800-2020)	14	1923	(1530-1940)	12
T1-4N2-3						
Glottis	1440	(1240-1700)	3	1738	(1550-1925)	2
Supraglottis	1760	(281-2180)	32	1760	(1760-1950)	3
Preoperative	1580	(248-2120)	37	1590	(1540-1940)	36
Postoperative	1600	(1540-1860)	40	1565	(1520-1930)	20

of the patients in group 1, compared to 1.6% in group 2. Primary radiation therapy was selected in 43% of the patients in group 1, compared to 76% in group 2. Planned preoperative radiation therapy was given in 8% in group 1, and in 14% in group 2, whereas postoperative radiation therapy was administered in 8% of the patients in both groups.

The radiation dosage was expressed in terms of CRE equivalents, based on the NSD concept, reducing time, dose and fractionation factors to a single value (3) (Table 4). The treatments were given 5 days a week. Standard dose in group 1 was 60 to 65 Gy at a daily dose of 2 Gy over a period of 6 to 6½ weeks, whereas it was generally somewhat higher in group 2 where doses up to 70 Gy over a period of 7 weeks were more common when primary radiation therapy was selected.

The statistical methods for the analysis of the local-regional tumor control rates were based upon the Fisher exact probability of χ^2 -tests and for the comparison of the survival rates employing a modification of the log-rank test (4). When calculating the absolute survival rate, no discrimination as to the cause of death was made. The corrected survival rate was based on counting only patients as dying from carcinoma of the larynx as deceased, while deaths from second primary malignancies or intercurrent disease were withdrawn from observation. None of the patients, except one, in group 1 was lost to follow-up. All patients in group 2 were followed, and the minimal follow-

up time in both groups was 5 years. The corrected survival rates gave the best illustration of the influence of therapy.

Some of the material in group 1 has been published previously (5-9).

Results

Local and regional tumor control according to clinical stage (Table 5)

T1N0. The local and regional tumor control was similar in the two groups and no significant difference could be demonstrated between primary radiotherapy and primary surgery. Surgical salvage was successful in 6 of 9 and 7 of 8 patients treated with primary radiation therapy, and in 4/7 patients treated with primary surgery (cordectomy, supraglottic or hemilaryngectomy). Total laryngectomy was the standard operation for rescue. The percentage of patients who retained their cancer-free larynx was similar in the two groups (87% and 88%) after primary radiotherapy and 75% after primary surgery. The death rates from cancer of the larynx were 4% (n = 3) in group 1 and 3% (n = 2) in group 2 following primary radiation therapy, and 9% (n = 4) after primary surgery.

T2N0. The local tumor control after primary radiation therapy was similar in the two groups, but lower than in stage T1N0 (68 and 67% respectively), but higher, (84%), after primary surgery. The regional control of the neck was

higher, however, after primary radiation therapy (95% in both groups) than after primary surgery (79%). The salvage rate by total laryngectomy with or without radical neck dissection was higher in group 1 than in group 2, but fewer patients could be offered the rescue operation, so that the final number of patients who could retain a cancer-free larynx was about the same in the 2 groups (68 and 65% respectively). The death rate from larynx cancer was 23% in group 1 but only 11% in group 2. The salvage rate after primary surgery was 17% (1/6); the larynx was retained free of cancer in 19% and the death rate from cancer of the larynx was 21%.

T3N0. The local control rate was 43% in group 1 and 71% in group 2 after primary radiation therapy. Only 2 of the 12 failures in group 1 were operated for salvage and both were rescued, compared to 5 of the 6 failures in group 2 of which all 5 were rescued. In group 1, 43% retained a cancer-free larynx, whereas in group 2, 71% survived with the larynx intact and free of cancer. Primary surgery was more effective than radiation therapy in group 1, resulting in a local control rate of 84%, but was less effective in controlling the neck node metastases than primary radiation therapy (71% versus 86% in group 1 and 95% in group 2). Three of 7 patients operated for salvage after primary surgery were rescued, and 7% retained a cancer-free larynx. The death rate from larynx cancer was 52% in group 1 after primary radiation therapy and 24% after primary surgery but only 10% after primary radiation therapy in group 2.

T4N0. The local control rate after primary radiation therapy was 23% in group 1 compared to 40% in group 2, and the corresponding regional control rates were 77% and 90%. Very few of the failures could be operated. The percentage of patients retaining the larynx was 23% in group 1 compared to 40% in group 2. The death rates from larynx cancer were 77% in group 1 and 50% in group 2, which were similar to those observed after primary surgery. The local control rates were superior with primary surgery (78 and 75% respectively) but the regional control of the neck was inferior to that observed after primary radiation therapy (56% in group 1 and 75% in group 2 versus 77% in group 1 and 90% in group 2).

N1. Both the local and the regional control rates were substantially higher in group 2 (67 and 87% respectively) than in group 1 (18 and 24%) after primary radiation therapy with a larger number of patients retaining a cancer-free larynx in group 2. The death rates from cancer of the larynx was 88% in group 1 compared to 47% in group 2. Primary surgery produced a local control rate of 84%, but a lower control rate of the neck (56%). The death rate from cancer of the larynx was 53%, which was of the same order of magnitude as that observed after primary radiation therapy in group 2 (47%).

N2N3. Even though 6/9 patients obtained local control after primary surgery, the regional problem of control of

metastatic nodes in the neck remained and the death rate from cancer of the larynx was high regardless of mode of therapy (78% to 89%).

Survival. The computer plot of the absolute survival of the entire patient population under review in the two groups showed significant differences (Fig. 1). The 5-year survival was 45% in group 1, compared to 60% in group 2. The corrected survival curves depicted even more significant differences ($p < 0.00001$) with a 5-year survival of 60% in group 1 and 78% in group 2 (Fig. 2). In patients with glottic carcinomas, the corrected survival curves showed significantly better survival in group 2 than in group 1 and the 5-year survival rates were 90 and 78% respectively (Fig. 3). Also for carcinoma of the supraglottic region there was significantly better survival in group 2 than in group 1 with 5-year survival rates of 60% and 45% respectively (Fig. 4). The influence of the patients' age is illustrated in Figs 5–7. Patients less than 50 years of age had a 5-year survival rate of 67% in group 1 compared to 95% in group 2. In the group of patients of age 51–70, even more significant differences were noted with the 5-year survival of 60% in group 1 compared to 80% in group 2 ($p < 0.00001$). In the group of patients beyond the age of 70, however, no difference in survival was noted when comparing the 2 groups.

Sex was also a significant factor: In men, the 5-year survival rate was 60% in group 1 compared 79% in group 2 ($p < 0.00001$) (Fig. 8), but in women no difference was observed (Fig. 9).

Clinical stage was of great importance; No difference in the corrected survival was noted in the early stages (T1N0T2N0) (Figs 10–15). The 5-year survival was 98–99% in patients with T1N0 glottic tumors, with a slightly lower survival for patients with supraglottic tumors. Patients with T2N0 tumors had a somewhat lower survival in both groups (82% and 86%) than those with T1N0 tumors. Patients with supraglottic tumors had again a lower survival (72% and 81% at 5 years) than those with glottic tumors of the same stage.

Significant differences in the corrected survival curves appeared in the groups of patients with T3N0 tumors (Fig. 16): The 5-year corrected survival was 59% in group 1 compared to 84% in group 2. In patients with glottic T3N0 tumors (Fig. 17), the corresponding survival rates were 58% and 82%, but in patients with supraglottic T3N0 tumors (Fig. 18), the difference in the survival curves did not reach statistical significance probably due to the small numbers of patients in the groups, even though the 5-year corrected survival rate was only 51% in group 1 compared to 76% in group 2.

The patients with T4N0 tumors also showed significantly better corrected survival in group 2 than in group 1 (Fig. 19) with the 5-year survival rates of 70% and 45% respectively. Preoperative or postoperative radiation therapy in patients with T4N0 tumors seemed to improve the

Table 5
Squamous cell carcinoma of the larynx

Stage	Primary treatment	Tumor control, Local		Tumor control, Regional		Surgical salvage		Cancer-free larynx retained		Died of ca. larynx		Died of 2. prim. cancer		Died of intercurrent dis.	
		UW	RH	UW	RH	UW	RH	UW	RH	UW	RH	UW	RH	UW	RH
T1N0	Radiotherapy	61/70 87%	64/73 88%	70/70 100%	72/73 99%	6/9	7/8	61/70 87%	64/73 88%	3/70 4%	2/73 3%	13/70 19%	5/73 7%	25/70 36%	19/73 26%
	Surgery	36/44 82%	0/0	41/44 93%	0/0	4/7	0/0	33/44 75%	0/0	4/44 9%	0/0	7/44 16%	0/0	17/44 39%	0/0
	Preop. radiother.	0/0	1/1	0/0	1/1			0/0	0/1	0/0	0/1	0/0	0/1	0/0	0/1
	Postop. radiother.	1/1	0/0	1/1	0/0			0/1	0/0	0/1	0/0	0/1	0/0	1/1	0/0
T1N0	Total	98/115 85%	65/74 88%	112/115 97%	73/74 99%	10/16 63%	7/8 88%	94/115 82%	64/74 86%	7/115 6%	2/74 3%	20/115 17%	5/74 7%	43/115 37%	19/74 26%
T2N0	Radiotherapy	30/44 68%	42/63 67%	42/44 95%	60/63 95%	7/8	15/21 71%	30/44 68%	41/63 65%	10/44 23%	7/63 11%	10/44 23%	7/63 11%	15/44 34%	20/63 32%
	Surgery	36/43 84%	0/0	34/43 79%	0/0	1/6 17%	0/0	8/43 19%	0/0	9/43 21%	0/0	5/43 12%	0/0	15/43 35%	0/0
	Preop. radiother.	1/1	0/1	1/1	0/1		1/1	0/1	0/1	0/1	0/1	0/1	0/1	1/1	1/1
	Postop. radiother.	3/3	0/0	3/3	0/0			0/3	0/0	0/3	0/0	1/3	0/0	2/3	0/0
T2N0	Total	70/91 77%	42/64 66%	80/91 88%	60/64 94%	8/14 57%	16/22 73%	38/91 42%	41/64 64%	19/91 21%	7/64 11%	16/91 18%	7/64 11%	33/91 36%	21/64 33%
T3N0	Radiotherapy	9/21 43%	15/21 71%	18/21 86%	20/21 95%	2/2	5/5	9/21 43%	15/21 71%	11/21 52%	2/21 10%	2/21 10%	2/21 10%	8/21 38%	9/21 43%
	Surgery	36/42 86%	0/0	30/42 71%	0/0	3/7		3/42 7%	0/0	10/42 24%	0/0	4/42 10%	0/0	14/42 33%	0/0
	Preop. radiother.	4/4	9/9	3/4	7/9			0/4	0/9	1/4	1/9	0/4	1/9	1/4	0/9
	Postop. radiother.	1/1	3/3	1/1	2/3		0/1	0/1	0/3	1/1	2/3	0/1	1/3	0/1	0/3
T3N0	Total	50/68 74%	27/33 82%	52/68 76%	29/33 88%	5/9 56%	5/6 83%	12/68 18%	15/33 45%	23/68 34%	5/33 15%	6/68 9%	4/33 12%	23/68 34%	9/33 27%
T4N0	Radiotherapy	5/22 23%	4/10 40%	17/22 77%	9/10 90%	1/3	1/3	5/22 23%	4/10 40%	17/22 77%	5/10 50%	3/22 14%	0/10	0/22	1/10 10%
	Surgery	21/27 78%	3/4 75%	15/27 56%	3/4 75%	0/3	0/1	0/27	0/4	14/27 52%	2/4 50%	4/27 15%	0/4	3/27 11%	2/4 50%
	Preop. radiother.	7/10	7/7	6/10	7/7	0/1		0/10	0/7	5/10	0/7	0/10	2/7	4/10	1/7
	Postop. radiother.	11/16	10/10	10/16	9/10	0/2	0/1	0/16	0/10	9/16	1/10	1/16	1/10	2/16	4/10
T4N0	Total	44/75 59%	24/31 77%	48/75 64%	28/31 90%	1/9 11%	1/5 20%	5/75 7%	4/31 13%	45/75 60%	8/31 26%	8/75 11%	3/31 10%	9/75 12%	8/31 26%
Any TN1	Radiotherapy	3/17 18%	10/15 67%	4/17 24%	13/15 87%		2/2	3/17 18%	10/15 67%	15/17 88%	7/15 47%	2/17 6%	1/15 7%	0/17	0/15
	Surgery	27/32 84%	0/0	18/32 56%	0/0	3/5		2/32 6%	0/0	17/32 53%	0/0	5/32 16%	0/0	7/32 22%	0/0
	Preop. radiother.	9/13 69%	7/10 70%	6/13 46%	8/10 80%	0/1	0/2	0/13	0/10	9/13 69%	7/10 70%	1/13 8%	2/10 20%	1/13 8%	0/10
	Postop. radiother.	7/11 64%	3/5 60%	6/11 55%	4/5 80%	0/1	0/1	0/11	0/5	5/11 45%	4/5 80%	4/11 36%	1/5 20%	2/11 18%	0/5
Any TN1	Total	46/73 63%	20/30 67%	34/73 47%	25/30 83%	3/7 43%	2/5 40%	5/73 7%	10/30 33%	46/73 63%	18/30 60%	12/73 16%	4/30 13%	10/73 14%	0/30
Any TN2N3	Radiotherapy	6/35 17%	2/5 40%	6/35 17%	2/5 40%			3/35 9%	1/5 20%	31/35 89%	4/5 80%	1/35 3%	0/5	3/35 9%	1/5 20%
	Surgery	6/9 67%	0/0	1/9 11%	0/0	1/5		0/9	0/0	7/9 78%	0/0	1/9 11%	0/0	1/9 11%	0/0
	Preop. radiother.	3/9	7/8	4/9	3/8	0/1	0/2	0/9	0/8	7/9	7/8	0/9	1/8	1/9	0/8
	Postop. radiother.	6/8	2/2	2/8	1/2			0/8	0/2	7/8	2/2	1/8	0/2	0/8	0/2
Any TN2N3	Total	21/61 34%	11/15 73%	13/61 21%	6/15 40%	1/6 17%	0/2	3/61 5%	1/15 7%	52/61 85%	13/15 87%	3/61 5%	1/15 7%	5/61 8%	1/15 7%
Grand Total		329 483 68%	189 247 77%	339 483 70%	221 247 89%	28 61 46%	31 48 65%	157 483 33%	136 247 55%	192 483 40%	53 247 21%	65 483 13%	24 247 10%	123 483 25%	58 247 23%

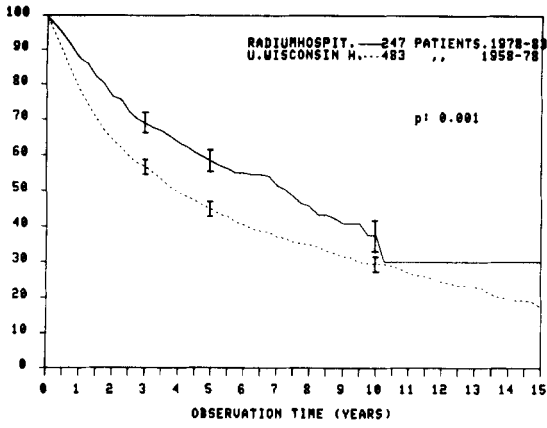


Fig. 1. Absolute survival. Total material.

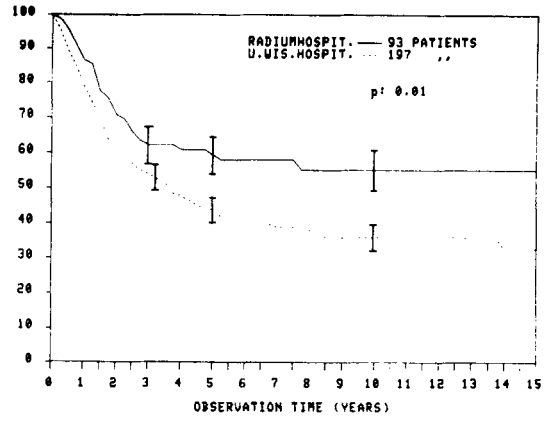


Fig. 4. Corrected survival. Supraglottic cancer.

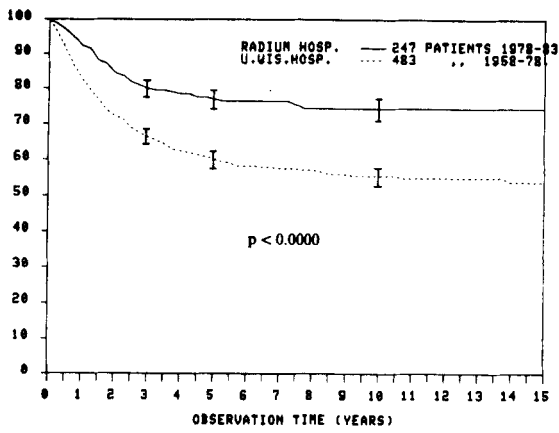


Fig. 2. Corrected survival. Total material.

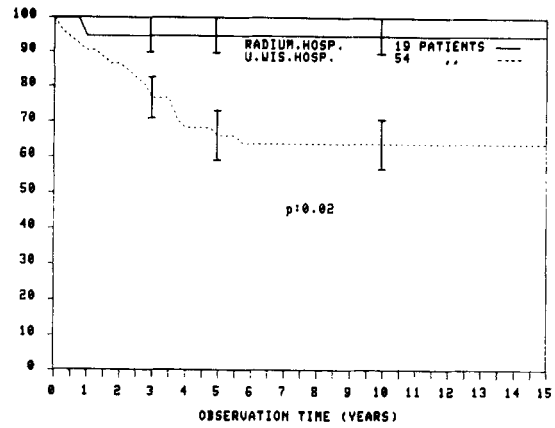


Fig. 5. Corrected survival. All patients with age < 50 years.

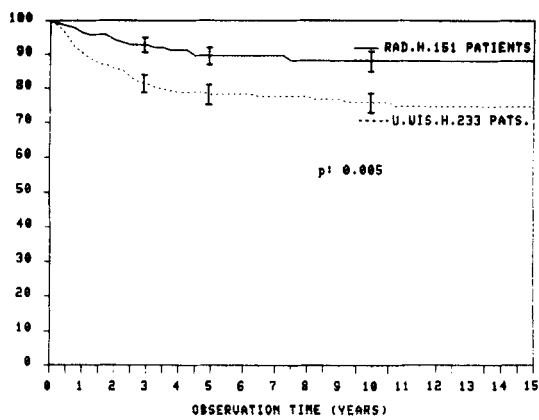


Fig. 3. Corrected survival. Glottic cancer.

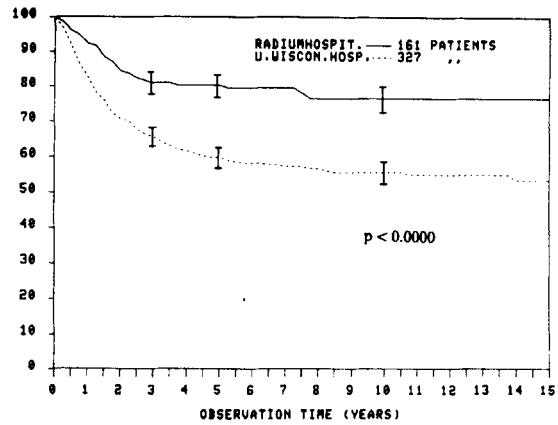


Fig. 6. Corrected survival. All patients aged 51-70 years.

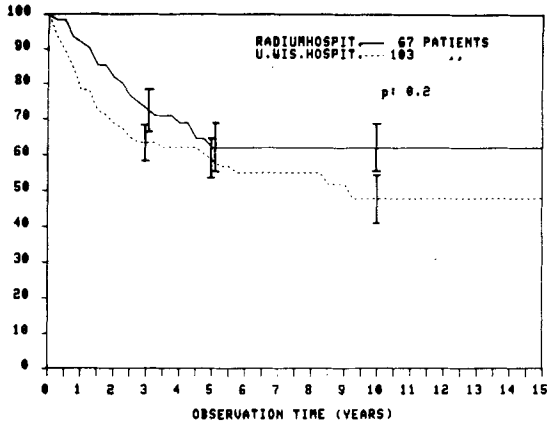


Fig. 7. Corrected survival. All patients ≤ 70 years.

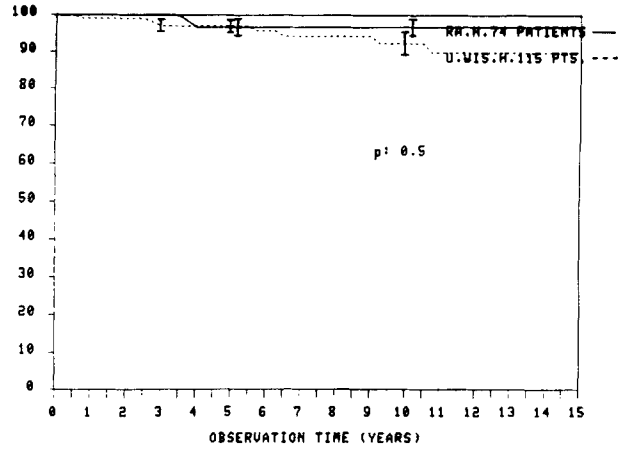


Fig. 10. Corrected survival. All T1N0 tumors.

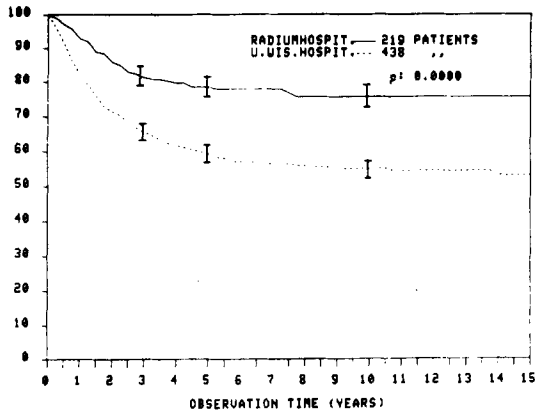


Fig. 8. Corrected survival. Males.

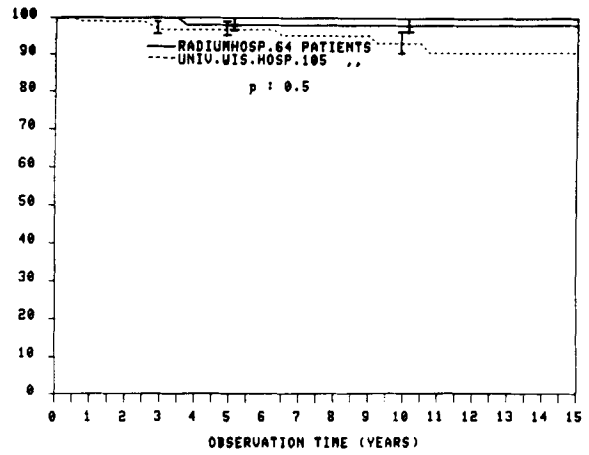


Fig. 11. Corrected survival. Glottic T1N0 cancer.

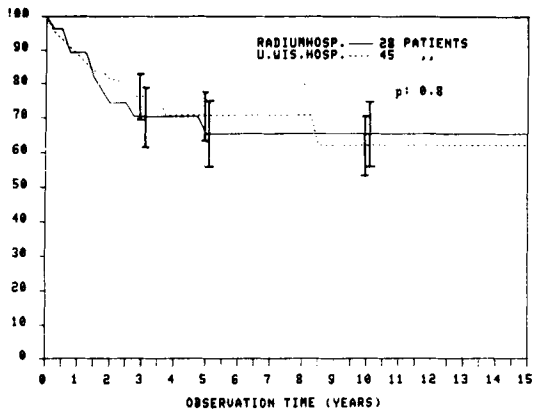


Fig. 9. Corrected survival. Females.

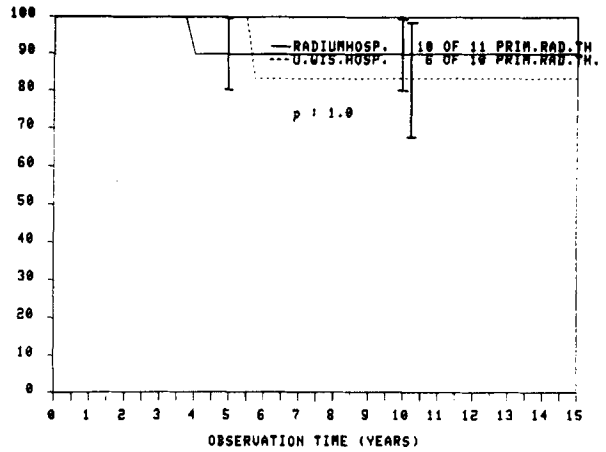
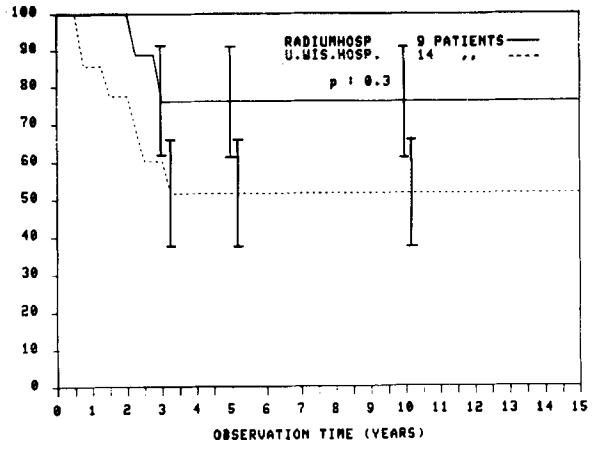
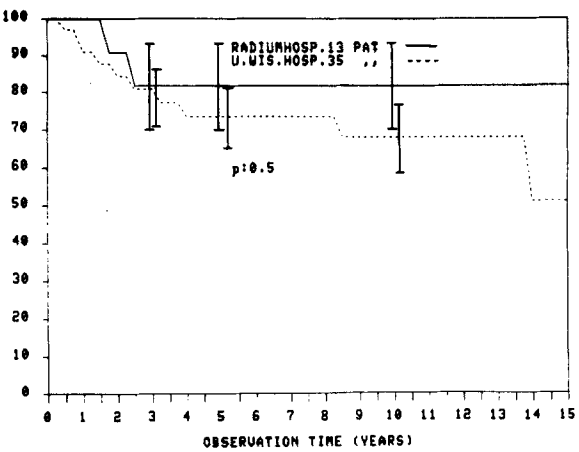
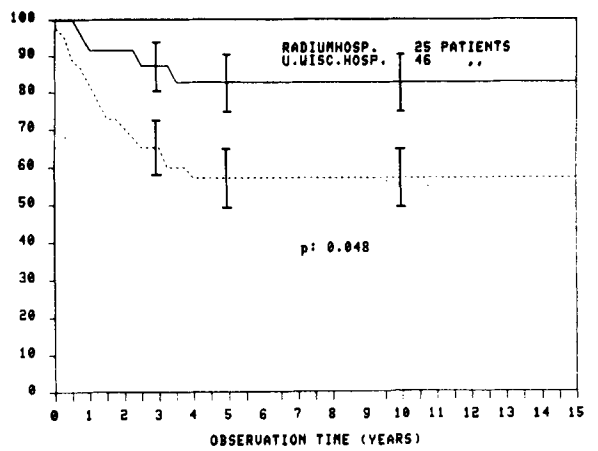
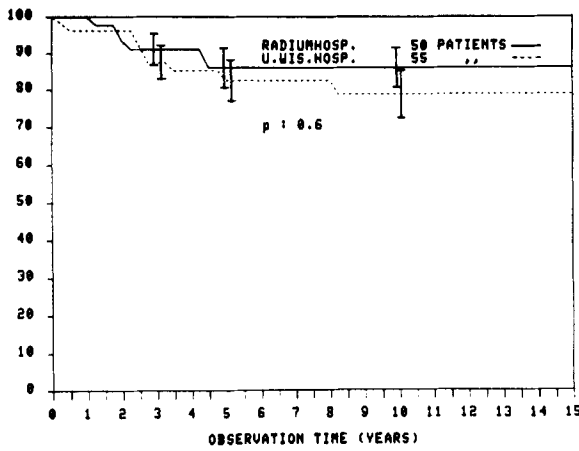
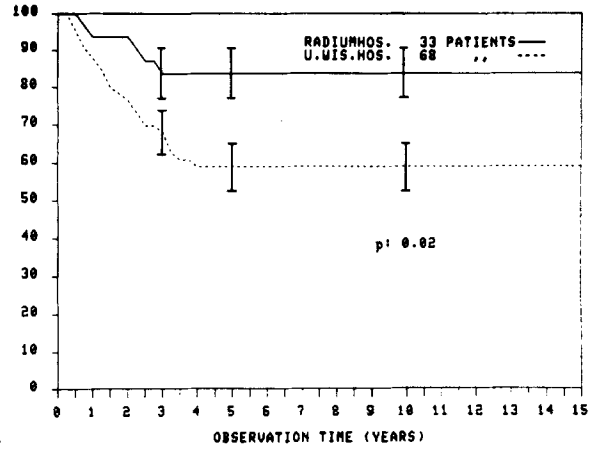
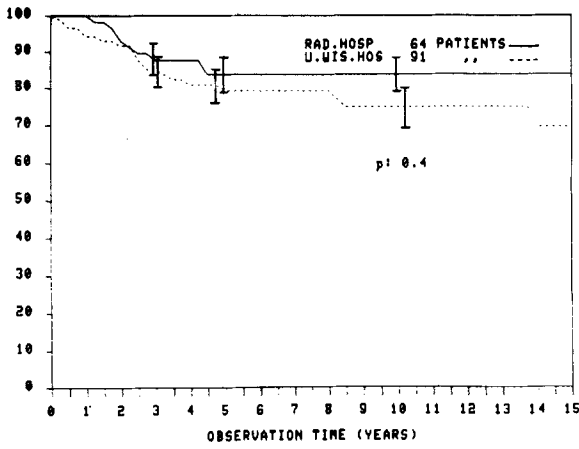


Fig. 12. Corrected survival. Supraglottic T1N0 cancer.



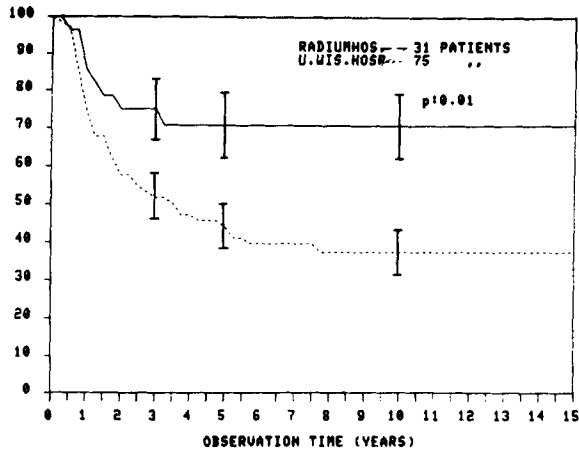


Fig. 19. Corrected survival. All T4N0 cancers.

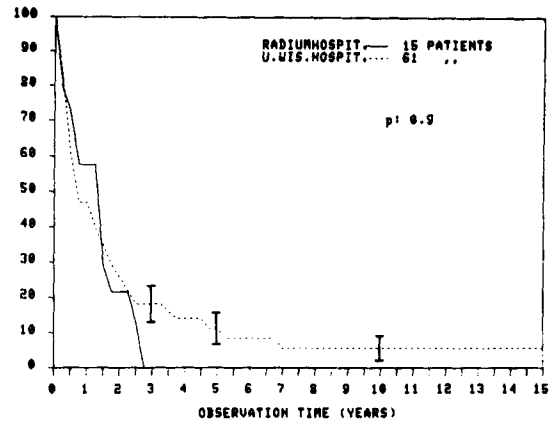


Fig. 22. Corrected survival. All N2 and N3 tumors.

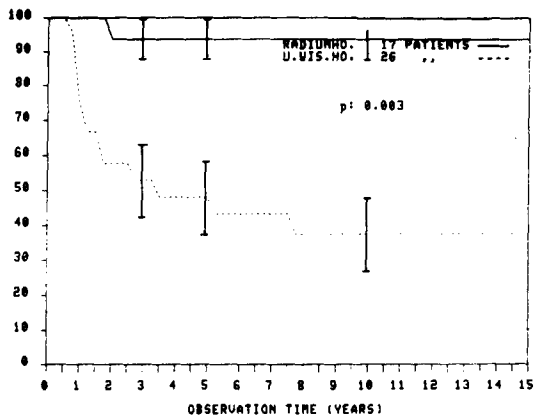


Fig. 20. Corrected survival. T4N0 tumors with pre- or postoperative radiotherapy.

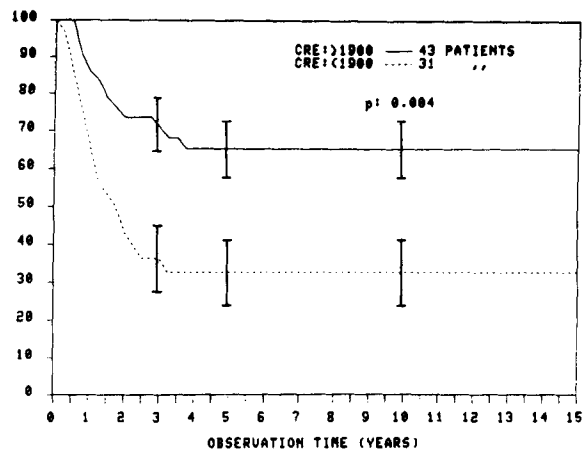


Fig. 23. Corrected survival according to radiation dosage (CRE values) in T3N0 and T4N0 tumors.

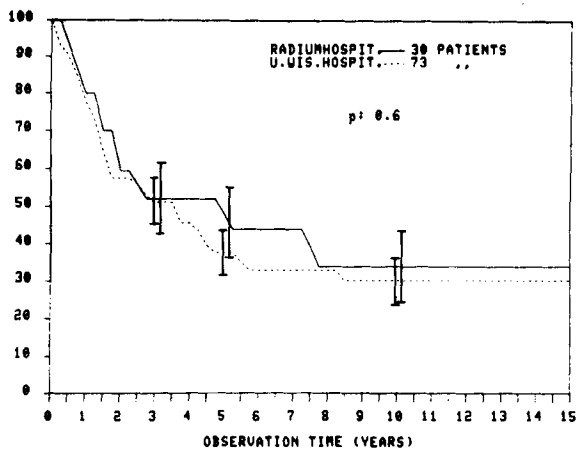


Fig. 21. Corrected survival. All N1 tumors.

survival significantly (Fig. 20) with the 5-year corrected survival rate of 94% in group 2 compared to only 50% in group 1 ($p = 0.003$).

No significant difference in the corrected survival was noted in patients with lymph node metastases in the neck. In patients with mobile, unilateral node metastases, the 5-year survival was 38% in group 1 and 43% in group 2. (Fig. 21). In patients with fixed nodes, the survival was dismal (Fig. 22). In patients with T3N0 and T4N0 tumors, the dose of radiation made a great difference: Those patients who had been treated with a dose equivalent to a CRE of less than 1900 had a relative 5-year survival of 33% compared to 65% in those who had received more than 1900 ($p = 0.004$) (Fig. 23).

Second malignant tumors (Table 5). The incidence of development of second malignant neoplasms was high in both groups; 98 (20%) in group 1 and 47 (19%) in group 2. Cancer of the lung was most frequent; 29 patients in group 1 and 18 cases in group 2. The death rates were 13 and 10% in the 2 groups respectively (Table 5).

Table 6
Complications after treatment for primary and recurrent squamous cell carcinoma of the larynx

Radiotherapy	Group 1. U. Wis. Hosp. (209 patients treated)						Group 2. Radium Hosp. (187 patients treated)					
	Necr.	Fist.	Sten.	Bleed.	Edema	Total	Necr.	Fist.	Sten.	Bleed.	Edema	Total
Primary tumors	2	1	0	1	5 ^a	9/209	2	1	0	0	1	4/187
Recurrent tumors	0	3	0	0	0	3/209	2	2	1	0	0	5/187
Total	2	4	0	1	5	12/209 6%	4	3	1	0	1	9/187 5%
Surgery												
Primary	0	18	9	3	2 ^b	32/197	0	0	0	0	1	1/4
Recurrent	1	6	0	0	0	7/197	0	0	0	0	0	0/0
Total	1	24	9	3	2	39/197 20%	0	0	0	0	1	1/4
Preop. radiother.												
Primary tumors	3	6	1	1	0	11/37	0	6	0	0	0	6/36
Recurrent tumors	0	2	0	3	0	5/37	1	1	0	0	0	2/36
Total	3	8	1	4	0	16/37 43%	1	7	0	0	0	8/36 22%
Postop. radiotherapy												
Primary tumors	2	5	2	0	0	9/40	0	0	0	0	1	1/20
Recurrent tumors	0	0	0	1	0	1/40	0	0	0	0	0	0/20
Total	2	5	2	1	0	10/40 25%	0	0	0	0	0	1/20 5%
Grand total	8	41	12	9	7	77/483 16% ^c	5	10	0	0	3	19/247 8% ^c

^a Including 1 with pneumonia and 1 with Lhermitte's syndrome.

^b Including 1 with pneumonia

^c $p = 0.003$

Death from intercurrent diseases (Table 5). Among patients who had been successfully treated for carcinoma of the larynx, 25% and 23% of the total number of patients in the 2 groups died from other causes.

Complications (Table 6). Complications after primary radiation therapy developed in 12 of 209 patients (6%) in group 1 and in 9 of 187 patients (5%) in group 2. Necroses were observed in 2 and 4 patients, and fistulae in 4 and 3 patients respectively.

Primary surgery was associated with complications in 39 of 197 patients (20%) in group 1 and in 1 of 4 patients in group 2. The most frequent complications were fistulae ($n = 24$) and stenoses ($n = 9$) in group 1.

Preoperative radiation therapy was associated with the highest complication rates: 16 of 37 (43%) in group 1 and 8 of 36 (22%) in group 2. Fistulae, bleeding and necroses in group 1 and fistulae in group 2 were the most frequent complications.

Complications after postoperative radiation therapy occurred in 10 of 40 patients (25%) in group 1 and in none of 20 in group 2. Fistulae occurred in 5 patients in group 1. In summary, the complication rates decreased from 16% in group 1 to 8% in group 2. Four postoperative deaths occurred in group 1: respiratory arrest during tracheostomy, postoperative obstruction of tracheostoma,

fistula with attempted closure and shock with postoperative hypotension and cerebral edema were recorded. One patient in group 2 died from dehydration and nutritional deficiencies during radiation therapy.

Discussion

The limited value of comparing results based on retrospective chart reviews is acknowledged, particularly when different time periods are compared, even though most of the patients who received radiation therapy were under the supervision of the senior author. Much progress has been made during the last decades, both in radiotherapeutic and surgical techniques. Nevertheless, in the absence of prospectively randomized, multidisciplinary clinical trials, retrospective reviews do add to our knowledge. The basic question which was asked, was as follows: Is the traditional policy of primary radiation therapy, followed by frequent careful examinations and rescue surgery, if necessary, in the best interest of patients with squamous cell carcinoma of the larynx? Should primary surgery be offered to a larger number of patients, with or without pre- or postoperative radiation therapy?

The data may be interpreted as answers to these questions: Specifically, in an unselected group of patients from

a defined geographic area, no evidence has been presented to support the view that primary radiation therapy on principle is inferior to primary surgery, provided that the patients are followed carefully and rescue surgery can be done promptly in case of residual or recurrent tumor. In patients with early stage (mostly T1N0, T2N0), the results with optimal radiation therapy with surgery in reserve are at least equal to those obtained with primary surgery with respect to local-regional control and survival, but the laryngeal function is better preserved in a larger number of patients with primary radiation therapy. Also in more advanced tumors (T3N0, T4N0), primary radiation therapy, with surgery in reserve, may produce results which are comparable or even better in some patients than those produced by primary surgery with respect to local-regional control and survival with fewer complications and with better preservation of laryngeal function in those that are successfully irradiated.

If one accepts the thesis that primary radiation therapy, with surgery in reserve, resulted in better results in the present study in patients with T3N0, T4N0 tumors, one must ask for explanations. The data presented in Fig. 23 suggest that the dose of radiation might have been a factor. Table 4 shows that the median dose in patients with glottis tumors was lower in group 1 than in group 2 in all stages and in supraglottis tumors stages T1N0 and N1.

During the period covered by the study in group 1, the University of Wisconsin Radiotherapy Center was under development, and the cobalt-60 teletherapy unit was not installed until 1963. Wedge or compensation filters were not used routinely and dosimetry calculations were restricted to central axis depth dose determinations.

The extensive use of surgery alone in group 1 was associated with a high failure rate in the neck as evidenced by the data presented in Table 5: In patients with T2N0 tumors, surgery alone was associated with 9 neck node recurrences in 43 patients treated. Six underwent salvage operations, but only 1 could be rescued, so that altogether 8 patients failed in the neck. In patients with T3N0 tumors, 12 of 43 developed neck node recurrences after surgery alone. Three of 7 who underwent salvage operations, were rescued, but 9 died of regional failures. In patients with T4N0 tumors, 12 of 27 developed neck node recurrences, 3 underwent salvage operations, but none could be rescued, and all 12 patients died of regional failures. In patients with N1 tumors, 14 of 32 developed regional recurrences after surgery alone; 3 of 5 were rescued by operations, but 11 died of regional failures. In summary: 40 of 47 patients (85%) with neck node recurrences after surgery alone died, and the total failure rate due to regional metastases was 40 out of 144 patients (28%).

For comparison, only 7 of 109 (6%) patients treated with primary radiation therapy failed in the neck in group 2 (3 of 63 T2N0, 1 of 21 T3N0, 1 of 10 T4N0, and 2 of 15 N1).

Adjuvant pre- or postoperative radiation therapy also resulted in low regional failure rates; 8 of 45 (18%) (Table 5).

The importance of close observation with monthly examinations by experienced specialists after primary radiation therapy has been emphasized since most of the recurrences develop during the first 2 years (10–12). The surgical salvage rate was higher in group 2 (65%) than in group 1 (46%), contributing to improved survival rates. Delay in operations for salvage may lead to a larger number of unresectable recurrences and distant metastases. An important group of patients with obstructive symptoms require immediate surgery and were often treated with preliminary tracheostomy in group 1 followed by total laryngectomy. However, 39 of 71 such patients were deemed unresectable and were referred for radiation therapy. The overall local control rate in this group was 24% with 76% (54/71) expiring from carcinoma of the larynx. Total laryngectomy resulted in local control in 10, and regional control in 9. Only 2 patients died from larynx cancer. In group 2, only 3 patients underwent preliminary tracheostomy and 2 of them died of carcinoma of the larynx. The greater emphasis on immediate laryngectomy followed by postoperative radiation therapy may have been more successful in saving lives. The incidence of stomal recurrences has been high after preliminary tracheostomy (13), but the incidence can be reduced by postoperative radiation therapy to the lower neck (14, 15).

During the last few years, we have been successful in preventing tracheostomy by initiating therapy with dexamethasone, antibiotics with chemotherapy (cis-platinum + 5-fluorouracil), followed by low daily doses of radiation therapy up to 70 Gy total.

Carcinoma of the larynx is a curable disease. However, too many patients still die from it or live on with the handicaps of loss of laryngeal function due to the treatments. Certain principles are essential to the development of a rational approach to minimizing morbidity and mortality.

Early diagnosis leads to favorable conditions for treatment. A heavy responsibility rests with the primary physician who must refer the patient for diagnosis and appropriate treatment. Close cooperation must exist between the laryngologist and the radiation oncologist in joint clinics and conferences. Through exchange of information and experience, students, residents and staff can benefit, and a balanced evaluation can be presented to the patient, who will then be in a position to make an intelligent choice between the different options available. (16)

The selection of treatment should offer the best chance for local and regional tumor control with maximal survival, without sacrificing quality of life.

The treatments should be carried out with expertise, incorporating all the recent improvements in technique, based upon a thorough knowledge of the biologic behavior of the cancer and the potentials and limitations of the treatments.

The patients must be reexamined with frequent intervals following therapy by competent specialists so that residual or recurrent disease can be diagnosed at the earliest possible time and salvage therapy instituted. (17)

Rehabilitation with speech therapy, vocational, social and psychological readjustment must be instituted to insure the best possible quality of life. (18)

In order to achieve early diagnosis, education is the key issue. Medical students must get more training so that they become capable of diagnosing the carcinoma at the first examination or refer the patient promptly to the laryngologist. Residents must acquire knowledge to appreciate the potentials of different treatment modalities. Staff members of different specialties must develop joint projects to analyze results and develop better methods. Considering selection of treatment, one is confronted with a choice between 4 principal types of management options:

1. Primary radiation therapy in all patients except for those who require emergency procedures for obstructive symptoms. Surgery is reserved for those who have residual or recurrent carcinoma. The aim is to cure the disease with preservation of laryngeal function in the largest number of patients (19–25).

2. Surgical removal of all cancers; transorally in connection with microlaryngoscopy and biopsy by cord stripping, diathermy or laser for the tiny superficial in situ or focally microinvasive carcinomas limited to one vocal cord; cordectomy after laryngofissure in larger tumors on the mobile vocal cord; partial or hemilaryngectomy for still larger tumors confined to one side but infiltrating in depth; supraglottic, transverse partial laryngectomy for tumors confined to the epiglottis, aryepiglottic folds or false cord, with or without neck dissection; total laryngectomy for the advanced carcinomas with or without radical or elective node dissection of the neck (1, 26–32).

3. Planned pre- or postoperative radiation therapy with total laryngectomy \pm radical neck dissection in all advanced operable tumors in patients in satisfactory general condition. Patients with early carcinomas are usually irradiated primarily, with surgery kept in reserve (33–42).

4. The treatment method is selected for each individual patient after discussing with the patient and the participating physicians the different options available (43–45). This type of management integrates all the others and takes into account many factors such as the patient's general condition, any coexisting medical conditions, such as for instance chronic obstructive pulmonary disease with reduced vital capacity which might render the patient unsuitable for a supraglottic partial laryngectomy for fear of aspiration with repeated attacks of pneumonia, and the patient's own wishes such as retaining his or her voice, which might be more or less important depending on the patient's occupation. Voice quality after primary radiation therapy is generally superior to the quality after primary surgery. Jørgensen (46) observed that 90% (66/73) of the patients

successfully treated with roentgen therapy retained a normal or near normal voice, compared to 82% (22/28) after cobalt-60 megavoltage therapy. Technical factors might have played a role in reducing the success with cobalt irradiation. Woodhouse et al. (16) reported that 95% of the patients whose primary tumor was controlled by radiation therapy, retained a normal or slightly impaired voice (good to excellent in 86/147, fair in 44/147 patients with T1N0 lesions, good to excellent in 11/22, fair in 9/22 patients with T2N0 lesions and 4/6 and 2/6 respectively in T3T4 lesions, for a total of 111/175 (63%) good to excellent and 55/175 (32%) fair. Voice quality after irradiation depends on many factors such as fraction size and total dose of radiation, the stage of the tumor, and the life style of the patients. Studies at MD Anderson Tumor Institute indicate that 60 Gy delivered over a period of 5½ weeks in patients with superficial small vocal lesions is an optimal dose. Small exophytic lesions required 65 Gy in 6½ weeks, whereas large bulky T1 or T2 tumors were given 65 to 70 Gy in up to 7 weeks. (47) Further increase in dosage was associated with an increased incidence of edema and might negate the beneficial effects of radiation therapy on laryngeal function. Complications including necrosis were observed in 3 of 236 (1.3%) patients. The average dose in those 3 patients was equivalent to 1 950 ret. At Princess Margaret Hospital, Toronto, excellent results have been reported with a smaller dose (50 Gy in 4 weeks to 55 Gy in 5 weeks, 5 fractions a week for a total of 24 to 25 fractions (1 600 to 1 750 ret) (48).

Interviews were carried out with 129 of 192 patients irradiated 9 to 15 months previously. Among patients with T1 or T2 tumors, 79% had no or mild hoarseness, and 97% were able to communicate with no or mild distress. Patients with T3 or T4 tumors had retained ability to communicate with normal or near normal voice in 93% of the total number irradiated (49). The corresponding numbers for patients treated with surgery were 13% with no or mild hoarseness and 47% were able to communicate without much distress. Patients who continued smoking had a recurrence rate of 27% (13/48), compared to 14% (11/77) of those who stopped smoking. Similar results have been published from Amsterdam (50).

The extent of the tumor is also significant. The quality of voice is often less satisfactory in patients with more advanced tumors, because the tumors have frequently destroyed larger volumes of normal tissue and infiltrate deeply. Also the dose required for control has to be higher and edema with or without necrosis is more prevalent.

Patients with edema persisting more than 6 months after radiation therapy or progressing after 3 months usually have recurrent tumor (2, 51), but recurrent or residual tumor can be present without edema. In the study at University of California, San Francisco Medical Center, edema of the larynx after radiation therapy for carcinoma of the vocal cord, developed in 15% (38/247) (51). Edema

with persistent carcinoma was present in 25% (17/67). Edema without recurrence developed in 12% (21/180). Patients with protracted edema after radiation therapy may be difficult to evaluate since the tumor cells may persist in small nests and spread out in submucosal planes (52).

Biopsy and other trauma to the irradiated mucosa may precipitate infection and necrosis and may often be returned negative for tumor even though malignant cells may persist in depth. Some patients have to undergo total laryngectomy for chondronecrosis, and the operative specimen may be negative for malignant cells even on serial sections (52, 53). In the series studied at the University of Hong Kong, 9/26 operative specimens following total laryngectomy for postradiation edema were negative for malignant cells on histological examination (53).

The prognosis in patients with tumor-free specimens after secondary laryngectomy is good. In the series from the Boston Ear, Nose and Throat Associates, only 1 of 7 patients with glottic tumors originally died of the cancer. This patient had had a T2 lesion with subglottic extension and recurred in the mediastinum (52). Ten patients with T1 to T3 supraglottic carcinomas originally all survived more than 3 years, whereas the determinate survival of patients with T4 supraglottic lesions was 44% (7/16).

The maximal radiation tolerance of patients with early glottic carcinoma appears to be around 2 000 to 2 050 ret with conventional fractionation of 2 Gy a day (54), but patients with advanced carcinoma develop chondronecrosis more frequently due to underdiagnosed cartilaginous infiltration by tumor, perichondritis or soft tissue necrosis with infection. Differences of opinion regarding the subject of optimal doses in patients with different stages of carcinoma can be explained as related to the heterogeneity of tumors within each T-stage category. Tumor volume as well as depth of infiltration play a role. In studies from the University of Florida, early glottic tumors suitable for cordectomy were controlled with radiation therapy in 68 of 70 patients (97%) after a period of a minimum of 2 years of observation. In a group of patients with somewhat more extensive tumors considered suitable for hemilaryngectomy, radiation therapy produced a local control rate of 94% (79/84), whereas in a third group of patients with tumors too extensive for hemilaryngectomy or cordectomy, tumor control was obtained in 65% (36/55 T1T2 patients) (55). Similarly, at the University of Washington, St. Louis, among 177 patients with T1N0 glottic squamous cell carcinomas, radiation therapy controlled 83/101 (82%) tumors limited to one cord only, 18/23 (78%) when the anterior commissure was also involved, and 16/23 (70%) when both cords were involved (T1b). The voice was preserved in 93% of the patients with T1a and in 77% of those with T1b tumors (56). Similar observations were made at the Massachusetts General Hospital, where the 5-year corrected survival of patients with the tumor

confined to the anterior 2/3 of one vocal cord was 92% (191/208), when confined to both anterior 2/3 and anterior commissure 81% (34/42), but when involving entire cord or posterior 1/3 it was only 76% (57/75). In patients with normal cord mobility, but with extension into the supraglottic region, the 5-year tumor-free survival was 76% (22/29), with extension into the subglottic region 83% (10/12). The degree of mobility of the cord affects relative survival: When the cord showed impaired mobility, the 5-year survival was 73% (22/29) without extension, but with extension to the supraglottic region, it was only 58% (11/19).

Fixation places the tumor into the T3 category and decreased the relative 5-year survival to 27% (12/45) (20). The results from Amsterdam confirmed these findings: Patients with relatively small T2N0 tumors showed a local control rate of 96% at 2 years (22/23) with up to 68 Gy total dose and shrinking fields, compared to 65% (22/34) for those with large volume with or without impairment of mobility (56). Patients with very large tumors, but still within the T2N0 category, may require still higher doses.

The discussions regarding optimal dose of radiation in the different categories of the TNM classification system have centered on the shape of the dose-response curves. For early tumors the dose-response curve appears to be flat, apparently because the upper limit of dosages is near the plateau of the sigmoid curve (57). Larger tumors, particularly in the supraglottic area, may show a steep dose-response curve: the experience at MD Anderson Hospital and Tumor Institute in Houston showed that among 52 patients with T2 and T3 supraglottic tumors, the 2-year local control rate was 17% (1/6) for ret value around 1 700; 67% (10/15) for approximately 1 900 ret; 78% (18/23) for 2 000; and 88% (7/8) for about 2 100 ret, displaying a normal sigmoid response curve, expressed as a straight line on a probit-type logarithmic scale. (58) The group in Toronto described a relatively shallow dose-response curve in supraglottic carcinomas (59). The further investigation of factors influencing the response of tumors to radiation therapy include physical, biological and general systemic influences. Investigators in Finland (60) and Denmark (2, 61) have already pointed out that the hemoglobin levels in the blood of irradiated patients with carcinoma of the larynx are of importance.

The lymph nodes in the neck play an important role. The presence of metastases in the neck nodes reduces the chances for survival significantly, and extracapsular spread with fixation to carotid and jugular vessels or deep muscles presents the most difficult problems for both surgeons and oncologists (62). The prevention of node metastases is therefore of great importance. Neck node metastases are most prevalent in patients with supraglottic tumors. The presence of subclinical node metastases has been known and their eradication with elective radiation to the neck became apparent after analysis of the patient material at

MD Anderson Hospital (63). In patients in whom the primary tumor was controlled, and no palpable neck node metastases were found initially, the policy of irradiating the subdiaphragmatic and midjugular nodes electively with up to 50 Gy resulted in almost complete abolition of later development of neck node metastases. Only 1 patient recurred in the neck due to recurrence outside the borders of the radiation portal which was too small (64). Lymph node metastases also have an adverse effect on the probability of local control of the primary tumor (65). The extracapsular spread of tumor in metastatic neck nodes is another ominous sign: In a study at the University of Arkansas of 96 patients with supraglottic carcinoma who underwent radical neck dissection, death from carcinoma of the larynx occurred in patients without demonstrable lymph node metastases at a rate of 22% (8/36) which was the same as in patients who had node metastases without extracapsular spread (6/28) but much lower than in patients with histological evidence of extracapsular spread (16/32 = 50%) (66).

In summary, radiation therapy and surgery are complementary, but treatment policy differs in various institutions around the world depending on the past experiences and traditions developed within each geographic area. It is essential to accurately and completely record all data in a tumor registry. One may then at a later date analyze different factors which influence incidence and selection of treatment and the prognosis. With the advent of computers, such data can now be entered and stored for analysis at regular time intervals and compared with results from other institutions serving large populations in defined geographic regions. Only by such continuous comparison and feed-back of information can present treatment methods be modified to increase tumor-free survival and quality of life for our patients.

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