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Organ preservation by transoral laser microsurgery in piriform sinus carcinoma

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OBJECTIVE: To determine the effectiveness of organ-preserving CO₂ laser microsurgery for the treatment of piriform sinus carcinoma.

METHODS: A retrospective review of 129 previously untreated patients undergoing CO₂ laser microsurgery for the treatment of squamous cell carcinomas of the piriform sinus from 1981 to December 1996 was undertaken. The intention was complete tumor removal by preserving functionally important structures of the larynx. Distribution of tumors (Union Internationale Contre le Cancer/American Joint Committee on Cancer, 1992) was 24 cases with pT1, 74 with pT2, 17 with pT3, and 14 with pT4 disease. Node status was positive in 68% of patients. Seventy-five percent of patients had stage III or IV disease. Forty-two percent of the patients were treated solely with surgery, and 58% had surgery and postoperative radiotherapy. The median follow-up interval was 44 months.

RESULTS: Eighty-seven percent of patients were controlled locally. Neck recurrences occurred in 14.0% of patients, metachronous distant metastases with locoregional control in 6.2%, and second primary tumors in 18.6%. Twenty percent of patients died of TNM-related deaths. The 5-year overall Kaplan-Meier survival rate was 71% for stages I and II and 47% for stages III and IV disease; the 5-year recurrence-free survival rates were 95% and 69%, respectively.

CONCLUSION: A comparatively low local recurrence rate, a high recurrence-free survival rate, and the avoidance of laryngectomy favor function-preserving surgery of piriform sinus carcinomas. (Otolaryngol Head Neck Surg 2001;124:58-67.)

The poor prognosis of carcinoma of the hypopharynx has not improved during the last decades. The results of different treatment approaches have been extensively reviewed.^{1,2} The literature uniformly shows that the effect of recent advances in imaging technology, radiotherapy, surgery, and multimodality therapy on mortality has been largely disappointing.

The 5-year survival rates of patients with hypopharyngeal carcinomas of all tumor stages vary between 14% and 28% and rarely exceed 30% regardless of the treatment approach used. In 1998, a 5-year overall survival rate of 13% in 1012 patients with hypopharyngeal cancer treated mainly by primary radiotherapy over a 30-year period was reported from Scandinavia.³ The 1997 National Cancer Data Base Report on cancer of the head and neck communicated a 5-year disease specific survival of 31.4% in 3906 cases of hypopharyngeal carcinoma⁴ and of 33.6% in 822 cases of carcinoma of the piriform sinus.⁵

As radical surgery and postoperative radiotherapy could not improve the locoregional control rate and roughly one third of the patients die as a result of distant metastases, second primary cancers, and intercurrent diseases, it seems judicious to consider organ preservation therapy regimen to improve at least the quality of life in patients with a known unfavorable prognosis.² In recent years, there is a tendency toward conservative treatment. Organ-preservation strategies, radical radiotherapy alone, especially in early stages, and radiotherapy in combination with chemotherapy (neoadjuvant or concurrent) together with surgery, reserved only for the treatment of persisting or recurrent tumor, are under clinical evaluation.⁶

Carbon dioxide (CO₂) laser microsurgery has been used for the treatment of hypopharyngeal carcinomas in

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various centers in the United States, in India, and in Europe particularly in Germany. Reports about preliminary results have rarely been published and only about small numbers of cases. Since the early 1980s, we have preferred organ-preserving transoral lasermicrosurgical partial laryngopharyngectomy even in advanced lesions of the hypopharynx. Our first results of 36 transorally treated patients were presented in 1985 and published in 1987,⁷ followed by a report on 42 patients treated from 1981 to 1986 at the ENT Department of the University of Erlangen/Nürnberg by the senior author (W.S.).¹ Between 1988 and 1999, we reported sequentially on the results of laser microsurgery in hypopharyngeal carcinoma.⁸⁻¹⁰ This report focuses on the results of 129 patients with carcinoma of the piriform sinus treated between 1981 and 1996. To the best of our knowledge, this report includes most cases published so far and is the first about long-term results.

PATIENTS AND METHODS

Patients

A total of 200 previously untreated patients with squamous cell carcinoma of the piriform sinus were treated from August 1986 to December 1996 at the Department of Otorhinolaryngology–Head and Neck Surgery of the University of Goettingen, Goettingen, Germany. Forty-seven patients with previous other malignant tumors, 1 patient with simultaneous distant metastases, and 14 patients with advanced neck disease (N3) neck disease, because neck disease was unresectable, were excluded from the analysis. A total of 138 patients were treated with curative intent. Forty-eight of them had advanced primary tumors not resectable with preservation of function and were treated by various protocols: radiochemotherapy, 28; laser debulking of the primary tumor followed by radiochemotherapy, 10; neoadjuvant chemotherapy followed by laser resection of the primary tumor, neck dissection, and radiotherapy, 3; open partial laryngopharyngectomy, 1; and total laryngectomy with partial pharyngectomy, 6. The remaining 90 patients were treated with transoral laser microsurgery on the primary tumor. To those patients, another 39 previously untreated patients with piriform sinus carcinomas were added, treated between 1979 and May 1986 at the Department of Otorhinolaryngology–Head and Neck Surgery of the University of Erlangen, Erlangen, Germany (surgeon W.S.). The results of those patients were published earlier.¹ The present report comprises a total of 129 patients. The patients ranged in age from 34 to 91 years (median age, 54 years). One hundred and sixteen were male and 13 were female.

Preoperative Examination

The routine preoperative examination included magnifying laryngoscopy, palpation, and, since 1989, ultrasonography of the neck nodes. CT or MRI was indicated mainly in advanced tumors and when the lateral wall of the piriform sinus was

involved, for detection of submucosal spread to the esophagus, the contralateral hemilarynx and to the soft tissues of the neck (carotid sheath) as well as for identifying extensive infiltration of the cricoid. This knowledge is of great importance for the surgical planning of a transoral procedure. For the exclusion of possible concomitant second primary tumors and distant metastases, bronchoscopy, esophagoscopy, chest radiograph and ultrasonography of the abdomen were performed. Panendoscopy was done together with the resection of the primary tumor. Pulmonary function tests were performed only in cases with a history of chronic obstructive lung disease.

Operative Technique

Optimum exposure and visualization of the larynx and the hypopharynx is crucial for a safe tumor resection.¹¹ The operations were carried out using a Heraeus Laser Sonics LS 500 laser coupled to the operating microscope. The focus diameter of the micromanipulator was 0.5 mm and the delivered laser energy was about 2080 to 3900 Watts per cm². The CO₂ laser coagulates vessels with a maximum diameter of 0.5 to 1 mm. Bleeding from large vessels was controlled by electrocautery. Only exceptional vessels were clipped. Since the early 1980s, we use a bivalved laryngopharyngoscope (Steiner's adjustable laryngopharyngoscope) for transoral laser microsurgery in the piriform sinus. Multiple changes of the position of the laryngoscope are necessary to achieve good visualization of the tumor and the surrounding healthy tissue during the entire operation.

The surgical and oncologic principles are the same for laser microsurgery as for conventional resections. The primary concern is the complete resection of the tumor. During laser microsurgery, decisions are made in accordance with the local spread of the tumor. Piriform sinus carcinomas are usually transected to enable the surgeon to estimate the depth of tumor penetration and to identify the relationship of the tumor to the adjacent normal tissues such as cartilage (blockwise resection). This can be seen very easily in previously untreated tumors on the cut surface under high magnification because of a markedly more severe carbonization in the tumor than in healthy tissues. In case of doubt, frozen section analysis is used. The lesion is resected until healthy tissue is found and an appropriate safety margin can be maintained. For carcinoma of the piriform sinus, we prefer a margin of at least 5 mm for small superficial tumors and 5 to 10 mm for larger tumors and those with a deeply infiltrating growth pattern and with submucosal spread. This unconventional surgical technique was introduced by Steiner in the early 1980s. The resected specimens were histopathologically examined by step serial sections by the technique previously published.¹²

In cases of exposed or resected thyroid cartilage, a perioperative antibiotic prophylaxis, usually with penicillin, was given. In addition, an intraoperative dose of corticosteroids (250 mg dexamethasone sodium phosphate) was administered

Fig 1. A, Piriform sinus carcinoma infiltrating the postcricoid, the arytenoid, and the supraglottic region. **B,** Postoperative status 8 months after laser microsurgery. Both vocal cords are mobile. Patients has been recurrence-free for 7 years.

in more extended resections to decrease the likelihood for laryngeal edema. After extended resections, a feeding tube was inserted under direct visual control by the surgeon through the laryngoscope at the end of the operation.

In our experience, a pharyngoesophageal stenosis has to be expected only if very little mucosa and cricopharyngeus muscle could be preserved during surgery for a circumferential tumor of the hypopharynx. In these rare cases, a thick feeding tube was inserted like a stent. A soft diet could be taken by these patients very early without aspiration, further reducing the risk of pharyngoesophageal stenosis.

Treatment of the Primary Tumor

All patients received transoral laser microsurgical resection of the piriform sinus carcinoma (Fig 1). Five (3.9%) patients were tracheotomized prophylactically after extended resections to prevent aspiration pneumonia. All patients reached normal laryngeal protective function and were decannulated.

Pathologic staging according to the 1992 Union Internationale Contre le Cancer/American Joint Committee on

Table 1. Distribution of pT and N/pN categories according to UICC/AJCC 1992 classification (n = 129)

pT category	N/pN category					Total
	N0/pN0	pN1	pN2a	pN2b	pN2c	
pT1	10	8	1	5	0	24
pT2	23	12	3	32	4	74
pT3	6	0	0	11	0	17
pT4	2	2	0	9	1	14
Total	41	22	4	57	5	129

Cancer (UICC/AJCC) classification was used for the primary tumor and the neck to permit comparison with the literature. The distribution of the UICC/AJCC 1992 pT and N/pN categories is shown in Table 1. The stage distribution was as follows: stage I, 10 (7.7%); stage II, 23 (17.8%); stage III, 26 (20.2%); stage IV, 70 (54.3%) cases.

According to the UICC/AJCC 1997 classification for carcinoma of the hypopharynx, 8 of 16 pT1 tumors had to be upstaged to pT2 (7 cases) or pT3 (1 case), respectively. Forty-four of 74 pT2 tumors had to be upstaged to the pT3 category. According to this classification, a tumor has to be staged pT4 in case of infiltration of the soft tissue of the neck (11 cases) or because of tumor invasion of the esophagus (3 cases).

The distribution of the histopathologic grading of the primary tumors was as follows: G1, 4.7%; G2, 65.9%; G3, 23.3%; G4, 5.4%; and in 0.8%, tumors were not graded.

Treatment of the Neck

One hundred and ten patients received either a unilateral (96 [74.4%] patients) or a synchronous bilateral (14 [10.9%] patients) mainly delayed neck dissection. Nineteen (14.7%) patients had no neck dissection. The time delay incurred had a mean interval of 10 days. The majority of the procedures were selective neck dissections with removal of the lymph nodes of the levels II and III (37.1%), or II, III, and IV (45.1%). Neck dissections were performed in 12.9% of the procedures as modified radical cases and in only 4.8% of procedures as radical neck dissection. Neck node metastases were histopathologically confirmed in 88 (68.2%) patients. One positive lymph node was found in 26 (20.2%) cases and in 62 (48.1%) cases, multiple positive lymph nodes were found. Metastases with extranodal spread were detected in 27.3% patients with tumor-positive necks.

Postoperative Radiotherapy

Six (18.2%) patients in stage I and II and 78 (81.3%) patients in stage III and IV underwent postoperative radiotherapy of the primary site and both sides of the neck. Indications for irradiation included advanced pT category of

the primary tumor with microscopically involved margins (R1 resection), one or more lymph node metastases, and lymph node metastases with extracapsular spread.

Statistical Methods

Follow-up data were available of all patients. The "Erlangen" patients were followed until December 1993, and the "Goettingen" patients until July 1999; patients from either group who died were followed until their death. The median follow-up period was 44 months (range, 3 to 137 months). Survival calculations were done by the Kaplan-Meier method.¹³ The overall survival time was defined as the interval between the date of surgery and the date of the last follow-up or date of death. For the determination of recurrence-free survival, intercurrent deaths and deaths as a result of second primary tumors as well as patients alive without recurrence were regarded as censored observations. Uncensored observations were regarded as local and neck recurrences, distant metastases, and TNM-related deaths. For the determination of the local control rate, neck recurrences and distant metastases, intercurrent deaths, and deaths as a result of second primary tumors as well as patients alive without recurrence were regarded as censored observations. Local and locoregional failure, failure from functional reasons, and TNM-related deaths were considered as uncensored observations.

RESULTS

Local Control

Twelve (9.3%) patients developed local and 5 (3.9%) patients locoregional recurrences (Table 2). One of the locoregional recurrences occurred in the contralateral piriform sinus 59 months after initial treatment. Local and locoregional recurrences were found after a median interval of 12 months after primary treatment (range, 4 to 59 months; mean, 18 months). The 5-year local control rate estimated according to Kaplan-Meier was 82% (95% confidence interval [66; 98]) for stage I and II disease and 69% (95% confidence interval [48; 72]) for stage III and IV disease.

Eleven patients with local or locoregional recurrences were treated with curative intent: 8 patients were treated by further transoral laser microsurgical resection with or without radiotherapy, 1 patient underwent open partial pharyngectomy, 1 patient total laryngectomy with partial pharyngectomy, and 1 patient was irradiated. Six of them were successfully salvaged (3 are alive without disease, 2 died of intercurrent disease and 1 died as a result of a second primary carcinoma), and 5 patients died of uncontrolled tumor. Another 5 patients were treated palliatively and died from cancer. In 1 patient the type of secondary treatment is unknown. This case was regarded as TNM-related death.

Table 2. Oncologic follow-up in patients with piriform sinus carcinoma (n = 129)

	Stage I and II (n = 33)		Stage III and IV (n = 96)	
	n	%	n	%
Local recurrence	2	6.1	6	6.3
Local recurrence and DM	0	0	4	4.2
Locoregional recurrence	1	3.0	3*	3.1
Locoregional recurrence and DM	0	0	1	1.0
Late neck metastases	2	6.1	6†	6.3
Recurrent neck metastases	0	0	4	4.2
Recurrent neck metastases and DM	0	0	6	6.3
D M	1	3.0	7	7.3
Second primary tumor	6	18.2	18	18.8

*1 located in the contralateral piriform sinus.

†3 occurred in the contralateral undissected neck side.

DM, Distant metastases.

Regional Control

The overall failure rate in the neck was 14.0% (18 of 129 patients). Late and recurrent neck metastases were observed after a median interval of 7 months after primary treatment (range, 1 to 59 months; mean, 13 months) (Table 2). Three (13.6%) of 22 patients with pN0 necks after initial treatment developed late neck metastases in the dissected neck; 1 patient was successfully salvaged by neck dissection and radiotherapy and is alive with no evidence of disease, 1 patient died from intercurrent disease, and for one, the cause of death is unknown. Two (10.5%) of the 19 patients who had no neck dissection developed metastases in the upper jugular nodes of the neck ipsilateral to the primary tumor; 1 of them was successfully treated but died of intercurrent disease and 1 died of uncontrolled disease in the neck. Three (2.3%) of 129 patients developed late metastases in the contralateral undissected neck. These patients were successfully treated with neck dissection and are alive without tumor. Ten (11.4%) of 88 patients with histopathologic positive neck nodes developed recurrent neck metastases in the dissected neck side. Six of them consecutively developed distant metastases. Only 1 patient was successfully salvaged and is free of tumor and alive. One patient died of intercurrent disease with neck recurrence, and 8 patients died from recurrent neck metastases.

Distant Metastases

The overall incidence of distant metastases was 14.7% (19 of 129 patients). After a median interval of 42 months (range, 8 to 48 months) to the primary treatment, 8 patients developed distant metastases in lung, liver, or bone without evidence of local or neck recur-

Table 3. Vital status

	Stage I and II (n = 33)		Stage III and IV (n = 96)	
	n	%	n	%
Alive, NED	19	57.6	37	38.6
Alive with tumor	0	0.0	1	1.0
TNM-related death	1	3.0	25	26.0
Death from intercurrent disease	9	27.3	17	17.7
Death from second primary tumor	4	12.1	14	14.6
Cause of death unknown	0		2	2.1

NED, no evidence of disease.

Table 4. Recurrence-free survival

	Years	Survival rate (%)	95% Confidence interval
Stage I and II	2	100	100; 100
	3	100	100; 100
	5	95	86; 100
Stage III and IV	2	89	82; 95
	3	83	75; 91
	5	69	58; 80

Table 5. Overall survival

	Years	Survival rate (%)	95% Confidence interval
Stage I and II	2	91	81; 100
	3	85	72; 97
	5	71	54; 87
Stage III and IV	2	75	66; 84
	3	66	56; 76
	5	47	36; 57

rence. Eleven patients with local, locoregional, or neck recurrences developed distant metastases (Table 2).

Second Primary Tumors

Second primary malignancies were diagnosed in 24 (18.6%) patients (Table 2). In 9 cases, the second primary cancer was located in the head and neck region. Two patients developed oral cavity carcinomas (1 oral tongue, 1 floor of the mouth, 30 and 36 months after primary treatment), and 7 patients developed oropharyngeal second primaries (2 at the base of the tongue, 37 and 53 months after primary treatment; 1 posterior oropharyngeal wall with a latency of 18 months; 4 tonsil/soft palate, 1 of them in the tonsil contralateral to the piriform sinus after 43 months, and 3 in the tonsil ipsilateral to the piriform sinus 10, 27, and 37 months after the primary treatment). In 12 cases,

the second primary tumors occurred in other locations (lung, 7; esophagus, 3; large bowel, 4; prostate, 1).

Survival

The causes of death are listed in Table 3. The recurrence-free 5-year survival rates were 95% for stages I and II and 69% for stages III and IV, respectively (Table 4). The overall 5-year survival rates were 71% for stage I and II and 47% for stages III and IV (Table 5). The Kaplan-Meier estimates of recurrence-free and overall survival are shown in Fig 2 and Fig 3.

Postoperative Complications

Major complications were defined as complication of treatment requiring surgical management. Five (3.9%) patients experienced postoperative endolaryngeal hemorrhage. In all cases, the bleeding could be stopped by further microlaryngoscopy and endoscopic electrocoagulation. One patient underwent a tracheotomy because of postoperative hemorrhage. One patient postoperatively developed an airway compromising laryngeal edema. The edematous mucosa was removed during microlaryngoscopy and the patient had an uneventful recovery. All wounds healed by secondary epithelialization, and there were no problems with perichondritis or chondritis despite the exposure of the thyroid cartilage in the majority of wound cavities.

Late Complications

One patient, who had a tumor resection extended to the esophagus, developed a hypopharyngeal stenosis. The patient is free of recurrence, without tracheotomy, normal voice and breathing and fed by a gastrostomy tube since 18 months.

Functional Results

Thirty-five (27.1%) patients achieved oral intake on the first postoperative day and had no nasogastric feeding tube. The median duration of nasogastric feeding in the remaining 94 (72.9%) patients was 7 days (range, 1 to 25 days; mean duration, 9 days). All but 2 patients achieved oral intake. These 2 patients had severe aspiration but refused laryngectomy, and they are fed by gastrostomy tubes. One of them has been dependent on the gastrostomy tube for 84 months, and the other for 54 months. One has a normal voice and breathing; the other also underwent a tracheotomy.

DISCUSSION

According to the recommendations of the United States National Cancer Institute (NCI),⁶ the standard treatment for hypopharyngeal cancer is a combination of radical surgery (bloc resection of the primary tumor

Fig 2. Kaplan-Meier estimates of recurrence-free survival after laser microsurgery of piriform sinus carcinoma (n = 129).

Fig 3. Kaplan-Meier estimates of overall survival after laser microsurgery of piriform sinus carcinoma (n = 129).

and the neck) and postoperative radiotherapy. The results of a survey conducted by Hoffman et al⁵ to identify standards of care for treatment of hypopharyngeal cancer revealed that about 44% of patients of all tumor stages had surgery with or without radiation therapy. Among the types of surgery used were 57.5% total laryngopharyngectomies and 25.3% partial laryngopharyngectomies or other local partial excisions; laser resections had been carried out in only 4%. Severe complications after combined treatment were observed in 6% to 34% and fatal complications in 2.4% to 14%.² The neoadjuvant chemotherapy followed by radiotherapy with the aim of organ preservation is noted by the NCI as "under clinical evaluation." The same definition

applies to unresectable stage IV hypopharyngeal carcinoma, where simultaneous chemoradiotherapy is compared with radiotherapy alone.

The 5-year disease-specific survival rates were reported by Hoffman et al⁵ as 63% for stage I, 58% for stage II, 42% for stage III, and 22% for stage IV hypopharyngeal cancers, regardless of the therapy. Their study demonstrated generally lower survival rates for early stage carcinoma treated with radiotherapy alone compared with surgery with or without adjuvant radiotherapy. Selection bias could not be identified.

Prerequisite for partial laryngopharyngectomy in piriform sinus cancer is the profound knowledge of the tumor growth patterns. In recent years, several histomorpholog-

ic studies on total laryngectomy specimens demonstrated that at least in a subgroup of patients partial laryngopharyngectomy with preservation of the contralateral uninvolvement hemilarynx would have been possible.¹⁴⁻¹⁶

Ogura et al¹⁷ were the first who described a larynx preserving surgical procedure in piriform sinus cancer. The 3-year survival rate achieved with partial laryngopharyngectomy in highly selected patients with early piriform sinus cancer (mobile arytenoid cartilage, apex of the sinus and thyroid cartilage free of tumor) was 59%; 34% of the patients lost their voices as a result of a secondary laryngectomy because of local recurrences.¹⁸ Ogura's indications were adopted by several laryngologists. Spector et al¹⁹ reported on the results of 408 patients, including the patients in Ogura's report, treated from 1964 to 1991 with various treatment strategies. To our knowledge, this report encompasses the largest number of cases (n = 207) treated with conservation surgery with and without preoperative or postoperative radiotherapy. The results achieved were excellent regarding local control and survival. The 5-year disease-specific survival rates ranged from 46% to 77% depending on location and extension of the tumor. The authors pointed out that these results might be due to an inherent selection bias because the most favorable lesions were treated by conservation surgery. However, complication rate and associated mortality rate were high. Since 1983, Spector's group used myocutaneous flap for reconstruction after the resection of medial wall tumors, and abandoned preoperative radiotherapy. This new strategy reduced the overall complication rate to 18.8% and the incidence of fatal complications to 4.6%.

Chevalier et al²⁰ reported the results of 31 patients with T1/T2 upper part piriform sinus cancer, treated between 1979 and 1994 with supraglottic hemilaryngopharyngectomy combined with radical neck dissection and postoperative radiotherapy. They achieved very good local control. However, the survival rates were relatively low, especially for the T2 cases, mainly because of a high rate of neck recurrences and distant metastases. All patients had a tracheotomy and tube feeding. In contrast, no patient treated with laser surgery with an early stage primary tumor needed a tracheotomy. The complication rate was much lower, and the functional results better. The same applies to the improved survival rates in our patients. Kraus et al²¹ reported on 39 cases, mainly piriform sinus cancer, treated by partial laryngopharyngectomy and radiotherapy. The local control rate was 79% and the 5-year disease-free survival rate was 54%. With the near total laryngopharyngectomy in appropriately selected patients with advanced disease as an alternative to total laryngectomy with partial pharyn-

gectomy, very satisfying oncologic and functional results were achieved.²²

Our results, obtained with transoral laser microsurgery combined with selective neck dissection and postoperative radiotherapy, demonstrate less perioperative morbidity and complications and no fatal complication. The recurrence-free and overall survival rates achieved by us were evidently better.

Primary radiotherapy (high dose treatment of the primary site and both sides of the neck to include the retropharyngeal and lateral cervical nodes) is regarded as an alternative to radical surgery, especially in early staged exophytically growing tumors located in the upper piriform sinus.^{6,23-25} Pameijer et al²⁶ reported the results of 23 T1 and T2 cases treated between 1984 and 1993. The 2-year local control rate was 78%. The local control rate decreased significantly when bulky apex disease was present or the tumor volume was more than 6.5ml. Garden et al²⁷ achieved a local control rate of 75.5% in 57 T1 and T2 carcinomas. Curative radiation therapy was applied only to the primary tumor. Wang²⁸ reported 5-year actuarial local control rates for T1 and T2 tumors of 74% and 76%, respectively. The 5-year disease specific survival rates were 73% for T1 and 68% for T2 cases. These favorable results are in contrast to 5-year tumor-specific survival rates of 40% and 28% for T1 and T2 tumors, respectively, reported by Jones.²⁵

For advanced disease, primary radical radiotherapy has yielded unfavorable results. The 5-year survival rates reported range from 5% to 30%.^{3,5,25,28} Factors, such as esophageal involvement, extension to the soft tissue of the neck, destruction of thyroid and/or cricoid cartilage, preclude the possibility of locoregional control by radiation alone.

The rates of organ preservation and the incidence of severe, especially fatal, complications may play an important role in evaluating different therapeutic approaches with similar oncologic results. The incidence of moderate and severe complications of radical high dose radiation therapy is between 5.5% and 18%.^{25,27-29} A temporary or permanent tracheotomy was frequently needed. Instead of a complete laryngectomy, secondary laryngectomy is possible in some patients.

It is a well-known fact that salvage surgery after primary radiotherapy frequently carries serious complications²⁹ and bad outcome. Rodriguez et al³⁰ reported on 160 patients with hypopharyngeal carcinomas who had salvage surgery, predominantly because of treatment failures or complications after radiotherapy. During the period from 1970 to 1990, the rate of lethal postoperative complications decreased from 25% to 8%. The crude survival rate was 15% at 5 years. Davidson et al³¹ reported on 108 patients who underwent salvage

surgery for recurrent disease after primary radiotherapy for advanced laryngopharyngeal carcinoma. Twenty-seven percent had complications, and the 3-year overall survival rate was 22%. In another study, only one third of patients were cured by salvage surgery.²⁷

In view of the complications of primary treatment and salvage surgery, even radiotherapists opted for early stage cancer for "surgery with a resection without functional and cosmetic mutilation."²⁸ This applies favorably to the transoral laser microsurgical resection of small piriform sinus carcinomas. The tumor can be removed very safely, preserving the larynx without the need for a feeding tube or for a tracheotomy, with superior local control and survival rates for stage I and stage II cases.

A new experimental approach for organ preservation in head and neck cancer treatment is 5-FU/cisplatin induction chemotherapy combined with radiotherapy regimens. A review of the trials carried out between 1970 and 1995 and of the published meta-analyses showed no clear evidence for an improvement in locoregional control and survival or decrease in the incidence of distant metastases.^{1,32,33} Nonetheless, induction chemotherapy for the treatment of advanced head and neck cancer patients has become a dominant common practice in the United States.³²

The only prospective randomized phase III trial comparing larynx-preserving chemotherapy and radiotherapy with radical surgery and radiotherapy, in hypopharyngeal cancer (resectable primaries stage II to IV) was conducted in Europe by the EORTC Head and Neck Cancer Cooperative Group and published in 1996.³⁴ Ninety-four patients were eligible for the "immediate surgery" arm and 100 patients for the "induction chemotherapy" arm of the study. Fifty-two (54%) of 97 patients with local disease and 31 (51%) of 61 with regional disease had a complete remission. About every other patient with complete remission of the primary tumor had a functional larynx after 5 years. Nonresponding patients underwent conventional surgery with postoperative irradiation. When patients relapsed after chemotherapy and irradiation, salvage surgery was performed. No differences were noted between the 2 arms concerning local, regional, and second primary sites. The rate of distant metastases was lower with 25% versus 36% in the chemotherapy arm. The 5-year disease-free survival rates were 36% in the surgery arm and 29% in the chemotherapy arm. The 5-year estimates of retaining a functional larynx were 35% of patients alive with a functional larynx if only death from local disease is considered as failure, and 17% if death from any cause is considered as failure. With respect to these results, the authors³⁴ concluded that larynx preservation without jeopardizing survival appears feasible in patients with cancer of the hypopharynx. On

the basis of these observations, the EORTC has now accepted the use of induction chemotherapy followed by radiation as the new standard treatment in its future phase III larynx preservation trials.

A critical analysis of the aforementioned study appears to be appropriate. For various reasons, only 52 of 100 patients completed the neoadjuvant chemotherapy arm, therefore only providing a small basis for final evaluation. There was a remarkably high incidence of complications, including 2 therapy-related deaths. Ninety-four percent of the patients had stage III and IV disease, including 38 patients with T2 lesions. Further included were patients with aryepiglottic fold tumors involving the hypopharyngeal aspect. It was stated that radical surgery would have been indicated for these patients and therefore the inclusion into the study was justified. According to the protocol, patients with a possibility of surgery for preserving functional larynx were excluded from participation. In our opinion, these exclusion criteria are highly subjective, and we would like to point out that for the patients mentioned above, organ preservation by means of partial laryngopharyngectomy (with or without laser) or by primary radiotherapy would have been possible.

Another approach for organ preservation is the application of neoadjuvant chemotherapy, partial laryngopharyngectomy, and postoperative radiotherapy. Laccourreye et al,³⁵ from 1964 to 1985, treated 34 patients with T2 carcinomas of the piriform sinus (without involvement of the preepiglottic space, the postcricoid region, and posterior wall), with a supracricoid hemilaryngopharyngectomy. Preoperative chemotherapy was given to 91% of the patients; 91% of the patients had postoperative radiotherapy. The disease control was excellent with 1 local recurrence, 2 neck recurrences, and 3 patients with distant metastases. The 5-year cause-specific survival rate was 55.8%. Two patients died of TNM-related causes, and 1 patient of radionecrosis.

Questions arise in that neither the clinical response to neoadjuvant chemotherapy nor the results of the histopathologic examination of the resection specimens were reported. There was a high incidence of therapy-related complications. The functional outcome was poor, eg, 7 (20%) patients had severe aspiration resulting in secondary pulmonary complications and necessitating temporary gastrostomy tube feeding in some patients. Completion laryngectomy from functional reasons was performed in 3 patients.

The impact of lymph node metastases in the neck on the prognosis of patients with piriform sinus carcinomas is well-known. The incidence of metastases at the time of initial presentation was 68.0% in our study; in 27.3% patients with tumor-positive necks, metastases with extracapsular spread (ECS) were present. These

observations are confirmed by others having reported similar figures.¹⁹ The French Cooperative Group of radiotherapists could impressively demonstrate that ECS was associated with poor prognosis.³⁶ The overall failure rate in the neck was 14.0% (18 of 129 patients) in our study. Three late neck metastases were observed in the dissected pN0 neck and 2 occurred in the initially untreated neck. The incidence of contralateral neck failures was low (2.3%, 3 of 129 patients). These patients had histopathologically proven metastases ipsilateral to the primary tumor and were all cured by further surgery. The incidence of metastases in the untreated or nonsurgically treated contralateral N0-neck has been reported to be 5% to 12%.^{21,37,38} Our data do not support the recommendation of routine use of bilateral neck dissections. Ten (11.4%) of 88 patients with tumor-positive necks developed recurrent neck metastases. The regional recurrence rate for the histopathologically tumor-positive neck is approximately 10%³⁹ and corresponds well to our findings.

It is well known that patients with hypopharyngeal cancer and lymph node metastases are, with increasing N-stage and the presence of ECS, increasingly at risk of developing distant metastases. The overall incidence of distant metastases in our study was 14.7%. In 10 of the patients, the failure at distant sites was correlated with failure to control the primary tumor and/or the neck. The reported incidence of distant metastases, mainly in the lung, bone, and liver, ranges from 10% to 27% depending on the extension and the localization of the tumor within the piriform sinus^{19,21,35,37} and the stage of neck disease. The rate of distant metastases identified in our study compares well with the published data.

In a meta-analysis of second primary tumors in head and neck cancer, a prevalence of 14.3% in 4550 cases of hypopharyngeal index carcinomas was found, with 40.8% located in the head and neck region, preferably in the oral cavity and the oropharynx, followed by lung, other locations, and esophagus.⁴⁰ On the basis of the rules given by Warren and Gates⁴¹ for the definition of multiple primary malignant tumors and considering a second tumor that developed at the same site a local recurrence, we found a similar incidence of 18.6% (24 of 129 patients) second primary tumors, with 37.5% located in the oral cavity or the oropharynx, followed by lung (29.2%), other locations (20.8%) and esophagus (12.5%). The prognosis of those patients was poor; the development of an infraclavicular second malignancy was almost always fatal. Twenty-five percent of all patients' deaths were due to second primary tumors.

CONCLUSIONS

Compared with radical radiotherapy, the results of

laser microsurgical treatment of early staged piriform sinus carcinoma are oncologically superior (local control and survival rates). Morbidity and rate of complications are lower, the functional outcome is similar, and the rate of larynx preservation is higher. The same applies to a comparison with the results reported for partial pharyngolaryngectomy with and without neoadjuvant chemotherapy or adjuvant radiotherapy, only that oncological results are similar while functional outcome is superior. As compared with standard therapy and new organ-preservation approaches (neoadjuvant chemotherapy and radiotherapy), our results in the treatment of advanced stage piriform sinus carcinoma are again oncologically superior; morbidity and rate of complications are lower, the organ preservation rate is higher. Our functional results were similar to those after neoadjuvant chemotherapy and radiotherapy, but better than those of standard therapy.

At present our results demonstrate only a positive trend towards better survival following organ-preserving surgery. Final proof of the effectiveness of the new therapeutic concept presented here requires well-designed prospective studies, with standardized surgical procedures carried out by head and neck surgeons skilled in laser surgery. The favorable results obtained so far by us with transoral laser microsurgery for early and advanced stages of piriform sinus carcinoma encourage us to continue using this organ-preserving and function-preserving approach.

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REFERENCES

- Steiner W. Treatment of hypopharyngeal carcinoma. *HNO* 1994;42:4-13,84-8,104-112,147-165.
- Allal AS. Cancer of the pyriform sinus: the trend towards conservative treatment. *Bull Cancer* 1997;84:757-62.
- Wahlberg PCG, Andersson KEH, Biörklund AT, et al. Carcinoma of the hypopharynx: analysis of incidence and survival in Sweden over a 30-year period. *Head Neck* 1998;20:714-9.
- Hoffman HT, Karnell LH, Funk GF, et al. The national cancer data base report on cancer of the head and neck. *Arch Otolaryngol Head and Neck Surg* 1998;124:951-62.
- Hoffman HT, Karnell LH, Shah JP, et al. Hypopharyngeal cancer patient care evaluation. *Laryngoscope* 1997;107:1005-17.
- National Cancer Institute: PDQ[®] treatment health professionals. July 1999. Available at: http://cancernet.nci.nih.gov/clinhy-popharyngeal_cancer_Physician.html.
- Steiner W, Herbst M. Combined therapy of hypopharyngeal carcinoma consisting of endoscopic laser surgery and postoperative radiotherapy. In: Sauer R, Schwab W, eds. Combined therapy of oropharyngeal and hypopharyngeal carcinoma. Baltimore: Urban & Schwarzenberg; 1987. p. 108-13.
- Steiner W. Therapy of hypopharyngeal carcinoma. In: Johnson JT, Didolkar MS, eds. *Head and Neck Cancer, Vol III. Proceedings of the Third International Conference on Head and*

- Neck Cancer, San Francisco, 26-30 July 1992. New York: Excerpta Medica. 1993. p. 101-9.
9. Steiner W, Ambrosch P. CO₂ laser microsurgery for hypopharyngeal carcinoma. In: Smee R, Bridger GP, eds. Laryngeal cancer. Proceedings of the 2nd World Congress on Laryngeal Cancer, Sydney, 20-24 February 1994. Amsterdam: Elsevier; 1994. p. 606-9.
10. Steiner W, Ambrosch P, Uhlig P, et al. CO₂ laser microsurgery for hypopharyngeal carcinoma. Proceedings of the 3rd European Congress of the European Federation of Oto-Rhino-Laryngological Societies "EUFOS," Budapest, 9-14 June 1996. Monduzzi Editore S.p.a. Bologna; 1996. p. 669-72.
11. Steiner W, Ambrosch P. Endoscopic laser surgery of the upper aerodigestive tract. New York: Georg Thieme; 2000.
12. Ambrosch P, Brinck U, Fischer G, et al. Special features of histopathological diagnosis in laser microsurgery of carcinomas of the upper aerodigestive tract. *Laryngorhinootologie* 1994;73:78-83.
13. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;58:457-81.
14. Dumich PS, Pearson BW, Weiland LH. Suitability of near-total laryngopharyngectomy in piriform carcinoma. *Arch Otolaryngol* 1984;110:664-9.
15. Zbären P, Egger Ch. Growth pattern of piriform sinus carcinomas. *Laryngoscope* 1997;107:511-8.
16. Glanz H. Pathomorphological aspects of transoral resection of hypopharyngeal carcinoma with preservation of the larynx. *Laryngorhinootologie* 1999;78:654-62.
17. Ogura JH, Jurema DA, Watson RK. Partial laryngopharyngectomy and neck dissection for pyriform sinus cancer. *Laryngoscope* 1960;70:1399-7.
18. Ogura JH, Marks JE, Freemann RB. Results of conservation surgery for cancers of the supraglottis and pyriform sinus. *Laryngoscope* 1980;90:591-600.
19. Spector JG, Sessions DG, Emami B, et al. Squamous cell carcinoma of the pyriform sinus: a nonrandomized comparison of therapeutic modalities and long-term results. *Laryngoscope* 1995;105:397-406.
20. Chevalier D, Watelet J-B, Darras J-A, et al. Supraglottic hemilaryngopharyngectomy plus radiation for the treatment of early lateral margin and pyriform sinus carcinoma. *Head Neck* 1997;19:1-5.
21. Kraus DH, Zelefsky MJ, Brock HAJ, et al. Combined surgery and radiation therapy for squamous cell carcinoma of the hypopharynx. *Otolaryngol Head Neck Surg* 1997;116:637-41.
22. Pearson BW, DeSanto LW, Olsen KD, et al. Results of near-total laryngectomy. *Ann Otol Rhinol Laryngol* 1998;107:820-5.
23. Bataini JP, Jaulerry C, Brunin F, et al. Significance and therapeutic implications of tumor regression following radiotherapy in patients treated for squamous cell carcinoma of the oropharynx and pharyngolarynx. *Head Neck* 1990;12:41-9.
24. Million RR, Cassisi NJ. Radical irradiation for carcinoma of the pyriform sinus. *Laryngoscope* 1981;91:439-50.
25. Jones AS. Tumours of the hypopharynx. In: Jones AS, Philipps DE, Hilgers FJ, eds. Diseases of the head and neck, nose and throat. New York: Oxford University Press, Inc; 1998. p. 230-49.
26. Pameijer FA, Mancuso AA, Mendenhall WM, et al. Evaluation of pretreatment computed tomography as a predictor of local control in T1/T2 pyriform sinus carcinoma treated with definitive radiotherapy. *Head Neck* 1998;20:159-69.
27. Garden AS, Morrison WH, Clayman GL, et al. Early squamous cell carcinoma of the hypopharynx: outcomes of treatment with radiation alone to the primary disease. *Head Neck* 1996;18:317-22.
28. Wang CC. Carcinoma of the hypopharynx. In: Wang CC, ed. Radiation therapy for head and neck neoplasms. New York: John Wiley & Sons, Inc; 1998. p. 205-20.
29. Mendenhall WM, Parsons JT, Stringer SP, et al. Radiotherapy alone or combined with neck dissection for T1-T2 carcinoma of the pyriform sinus: an alternative to conservation surgery. *Int J Radiat Oncol Biol Phys* 1993;27:1017-27.
30. Rodriguez J, Point D, Brunin F, et al. Surgery of the hypopharynx after radiotherapy. *Bull Cancer Radiother* 1996;83:17-23.
31. Davidson J, Keane T, Brown D, et al. Surgical salvage after radiotherapy for advanced laryngopharyngeal carcinoma. *Arch Otolaryngol Head Neck Surg* 1997;123:420-4.
32. Harari PM. Why has induction chemotherapy for advanced head and neck cancer become a United States community standard of practice? *J Clin Oncol* 1997;15:2050-5.
33. Lewin F, Damber L, Jonsson H, et al. Neoadjuvant chemotherapy with cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the head and neck: a randomized phase III study. *Radiother Oncol* 1997;43:23-8.
34. Lefebvre JL, Chevalier D, Lubinski B, et al. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer Phase III Trial. *J Natl Cancer Inst* 1996;88:890-9.
35. Laccourreye O, Merite-Drancy A, Brasnu D, et al. Supracricoid hemilaryngopharyngectomy in selected pyriform sinus carcinoma staged as T2. *Laryngoscope* 1993;103:1373-9.
36. Hofstetter S, Malissard L, N'Guyen TD, et al. Results of postoperative cervical node irradiation in carcinoma of the pharyngolarynx: a study of the cooperative group of radiotherapists. *Bull Cancer Radiother* 1996;83:86-9.
37. Johnson JT, Bacon GW, Myers EN, et al. Medial vs lateral wall pyriform sinus carcinoma: implications for management of regional lymphatics. *Head Neck* 1994;16:401-5.
38. Kowalski LP, Santos CR, Magrin J, et al. Factors influencing contralateral metastasis and prognosis from pyriform sinus carcinoma. *Am J Surg* 1995;170:440-5.
39. Leemans CR, Tiwari R, van der Waal I, et al. The efficacy of comprehensive neck dissection with or without postoperative radiotherapy in nodal metastases of squamous cell carcinoma of the upper respiratory and digestive tracts. *Laryngoscope* 1990;100:1194-8.
40. Haughey BH, Gates GA, Arfken CL, et al. Meta-analysis of second malignant tumors in head and neck cancer: the case for an endoscopic screening protocol. *Ann Otol Rhinol Laryngol* 1992;101:105-12.
41. Warren S, Gates O. Multiple primary malignant tumors: a survey of the literature and a statistical study. *Am J Cancer* 1932;16:1358-414.