were randomised to induction cisplatin and 5-FU followed by radiation therapy in complete responders and to surgery plus postoperative irradiation in non-responders or initial surgery and postoperative radiotherapy [12]. The 5-year rate of laryngeal voice preservation was 35% in the induction chemotherapy arm; there was no difference in the 5-year survival rates between the two treatment groups.

A caveat of both of these trials is that neither contained a radiation therapy alone arm so that it is difficult to know whether induction chemotherapy significantly increased the rate of laryngeal voice preservation over what might be achieved with radiation therapy alone. The Intergroup is currently conducting a randomised trial where patients with T2, T3, and T4 squamous cell carcinoma of the glottic or supraglottic larynx are randomised to (1) induction chemotherapy followed by radiotherapy in responders and surgery plus postoperative irradiation in non-responders; (2) radiation therapy and concomitant cisplatin; and (3) radiation therapy alone [4]. The radiation therapy regimen is 70 Gy in 35 fractions over 7 weeks in all three arms of the study. Hopefully, this study will better define the role of induction chemotherapy.

CONCLUSION

Limited non-randomised data indicate that a small subset of patients with early and moderately advanced glottic carcinomas may be cured with chemotherapy alone. Randomised trials indicate that a major response to induction chemotherapy may select a subset of patients who are more likely to be cured by radiation therapy with laryngeal voice preservation. Emerging data indicate that other parameters, such as the primary tumour volume calculated on pretreatment computed tomography, may be used for predicting the likelihood of local control after radiation therapy alone [3, 13]. Mendenhall and coworkers observed the following local control rates after irradiation alone in a series of patients with T3 glottic cancers: primary tumour volume $\leq 3.5\,cm^3$, 20 of 32 patients (87%) versus primary tumour volume $>3.5\,cm^3$, 4 of 14 patients (29%) (P=0.0005) [3]. It may be possible to select patients with favourable low-volume cancers for successful treatment with radiation therapy alone, and use induction chemotherapy to select patients from the high volume unfavourable subset who may be irradiated successfully with laryngeal voice preservation.

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INTRODUCTION

LARYNGEAL CANCERS comprise 2–4% of all malignancies diagnosed annually. With a prevalence of 55–75% among primary tumours, glottic carcinomas constitute the majority of laryngeal malignancies [1]. In the last decades, treatment options have included mostly surgery and radiotherapy, while chemotherapy has been relegated to palliative efforts for the patient with advanced disease [2]. More recent data suggest that chemotherapy may be useful as a single modality in the

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Table 1. *Review of published series*

First authors [ref.]	Period covered	Tumour stage	Number of chemotherapy cycles	Survival	IC	CCR	EC	Local control failure		'Cured' after EC
								EC	IC + surg	
Laccourreye [5]	1983–1991	T2	2–5	5 years 92%	67	17 (25%)	–	–	6%	–
Laccourreye [6]	1984–1991	T3T4	2–6	3 years 75%	20	Not stated	–	–	11%	–
Laccourreye [7]	1982–1991	T2	2–5	5 years 85%	94	31 (33%)	9	33%	8%	6
Laccourreye [8]	1985–1993	T1T2T3	4–15	3 years 92%	200	69 (35%)	25	30%	3%	18
Laccourreye [9]	1985–1992	T1T2T3	3–4	5 years 95%	178	58 (31%)	21	29%	3%	15
Laccourreye [10]	1983–1994	T1T2	3–10	5 years 83.5%	158	56 (35%)	25	32%	0%	17

IC, number of patients treated by induction chemotherapy; CCR, number of patients (percentage) with complete clinical response after induction chemotherapy; EC, number of patients treated by 'exclusive' chemotherapy.

effective treatment of T1–T3 glottic cancer. This relatively new therapeutic approach is discussed in light of the basics of glottic cancer.

CHEMOTHERAPY ALONE AS FIRST TREATMENT FOR GLOTTIC CANCER

Anatomy may explain the long-time local character of glottic cancer. Survival and organ preservation rates confirm the good therapeutic results of local therapies such as surgery and radiotherapy: 5-year cure rates of 85–93% for all T1 lesions include fair voice preservation in the vast majority of cases. Respective overall cure rates for T2 lesions are generally in the range between 70 and 80%. Conservation surgery is limited to those patients with subglottic extension less than 1 cm anteriorly and 3–4 mm posteriorly. T1 and T2 lesions with normal cord mobility may well be treated by either aforementioned modality. In fixed vocal cord T3 lesions, radiation therapy is less effective due to deep invasion. Cure rates are generally in the range of 30–60%. This percentage includes surgical salvage by total laryngectomy [3]. Despite widely diverging survival rates in the literature, T4 glottic cancers have a rather reserved prognosis and are treated by combined modality therapy including surgery, radiotherapy and/or chemotherapy [4].

In several retrospective, non-randomised trials (Table 1), Laccourreye and colleagues report their results of treating T1,T2,T3–N0N1–M0 glottic squamous cell carcinoma lesions by induction [5, 6] and/or 'exclusive' chemotherapy [7–10] with cisplatin and 5-fluorouracil: in the past, their innovative larynx surgery concepts [11] allowed them an excellent organ preservation rate of almost 100%. Their strategy was to add induction chemotherapy to partial laryngeal surgery or radiotherapy in the treatment of glottic cancer in order to increase survival and local control rate, as well as to reduce the rate of metastasis and second metasynchronous tumours [5]. In their trials 5-fluorouracil–cisplatin chemotherapy caused no reduction of organ metastasis and metasynchronous tumours. However, they observed that induction chemotherapy produced a 30–35% complete clinical response (CCR) with complete tumour disappearance and full vocal cord mobility. Moreover, CCR was associated significantly with complete histological remission [5, 7]. By meticulous follow-up strategies, they identified a small but constant subset of patients with long-lasting complete clinical remission after 5-fluorouracil–cisplatin was used as the only therapeutic modality. One-third of these patients developed a local relapse that could always be controlled by surgery. Thus, approximately 6–11% of patients were found to be cured by chemotherapy alone. In summary, chemotherapy did not have the expected systemic, but only local therapeutic effects producing CCR and complete histological remission in a small subset of patients.

The studies are limited by a number of issues: the patient selection for the respective study included, besides the T classification, additional clinical criteria not clearly established in the literature. The intra- and inter-study number of chemotherapy cycles varies (Table 1). The non-randomised, retrospective study design and the lack of confidential intervals exclude statistical evaluation. The relevant criteria for patients in CCR to be operated upon or to be treated by 'exclusive' chemotherapy (EC) remain unknown. No explanation is given for the constant 30% local recurrence rate after EC-CCR (complete clinical response after exclusive chemotherapy) in light of the highly significant correlation with complete histological remission. Besides the reports of Laccourreye and colleagues, no further data on this topic are available in the literature. However, the personal experience of many Ear, Nose and Throat (ENT) surgeons covers single cases of astonishing tumour response to chemotherapy, mostly in advanced cancers [12]. Retrospective identification of chemotherapeutically curable glottic cancer patients stands against the impossibility of predicting the individual clinical response. This drawback renders the set-up of conclusive prospective study designs rather difficult. A vulnerable but apparently infrequent biological behaviour pattern of the respective tumour might explain a complete tumour response to chemotherapy. Hopefully, genetic, molecular and/or cellular diagnostic tools will enable us to identify prospectively responsive patients in the near future [13]. At the moment, the observations of Laccourreye and coworkers reveal that the vast majority of patients with non-advanced glottic cancer treated by 5-fluorouracil–cisplatin chemotherapy receive insufficient treatment at considerable cost and with a risk of systemic side-effects.

Induction chemotherapy in advanced T3T4 glottic cancer aims first at organ preservation without compromising survival rates [14, 15]. No results are reported for 'exclusive' chemotherapy in T4 glottic cancer in the literature. Combined modality therapy dominates the published studies. A recent meta-analysis including 76 studies with more than 10 000 patients describes a small, but significant (4%/5 years) survival increase for the concomitant and no respective effect of adjuvant or induction-neoadjuvant chemotherapy in advanced squamous cell carcinoma of the head and neck [16]. The meta-analysis could not clarify the role of chemotherapy in larynx preservation.

CONCLUSION

The analysis of success and failure in the treatment of squamous cell cancer of the larynx is a difficult task because of the shortcomings of the actual staging system and the general lack of randomised prospective controlled studies. The indication to use the systemic approach of chemotherapy to solve the overwhelmingly local problem of non-advanced glottic cancer should be backed by statistical evidence of increased local control and survival. At the moment, there is no evidence that chemotherapy is a valid alternative to surgery and/or radiotherapy in non-advanced and little evidence in advanced glottic cancer. The patient even risks losing a potentially curative surgical option by tumour progression under chemotherapy. Chemotherapy should be used in well-defined, controlled clinical trials only—the most promising way to confirm potential advantages of chemotherapy in the local and systemic therapy concept of glottic cancer.

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TREATMENT OF head and neck cancer has traditionally been surgery and/or radiotherapy depending on the site and extent of the tumour. Chemotherapy has been reserved for palliation. In recent years, however, in order to improve loco-regional control, organ preservation and survival, induction chemotherapy has also been introduced in the multimodality treatment of head and neck including laryngeal cancers [1–6].

W. Mendenhall and M.A Holtz have expressed their opposing views regarding the impact of chemotherapy as first and single treatment for glottic cancer. Mendenhall is aware that only a small number of early-stage glottic cancers will be cured with chemotherapy alone, but expects to select by the tumour response potentially radiosensitive, otherwise unfavourable high-volume tumours for successful radiotherapy. Hotz however, argues that glottic cancer can effectively be treated by local therapies, therefore the use of chemotherapy means an insufficient treatment at a considerable cost and systemic side-effects.

Treatment of glottic cancer depends primarily on localisation and stage of the tumour, influenced by preferred treatment traditions originating from geography- and speciality-

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