Pergamon

European Journal of Cancer, Vol. 35, No. 9, pp. 1309–1313, 1999

Printed in Great Britain
0959-8049/99/$ - see front matter

PII: S0959-8049(99)00136-7

Current Controversies in Cancer

Should Chemotherapy Alone be the Initial Treatment for Glottic Squamous Cell Carcinoma?

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INTRODUCTION

CHEMOTHERAPY ALONE as the first step in the management of glottic cancer may either be used as the sole treatment or as induction therapy before radiation therapy and/or surgery. The goals of treatment include optimal local-regional control, improved survival, laryngeal voice preservation, and reduced complications and cost.

CHEMOTHERAPY ALONE

Very limited data exist pertaining to the role of chemotherapy alone for squamous cell carcinoma of the glottic larynx. Laccourreye and colleagues describe a series of 178 patients with T1–T3–N0 squamous cell carcinoma of the glottic larynx who received cisplatin and 5-fluorouracil (5-FU) chemotherapy between 1985 and 1992 [1]; 58 patients had a complete response. 21 patients had observation and 37 patients had a partial laryngectomy (35 patients) or radiation therapy (2 patients). The T-stage distribution of the chemotherapy-alone group was T1, 29%; T2, 52%; and T3, 19%. The 5-year actuarial local control and survival rates were 71% and 95%, respectively. Partial laryngectomy was possible in all patients who developed a local recurrence, so that the laryngeal preservation rate was 100%. No patient treated with chemotherapy alone died of laryngeal cancer. No patient experienced grade 4 toxicity.

Although these results are impressive and indicate that a subset of patients with early- and moderate-stage glottic cancer may be cured with chemotherapy alone, one must recall that a relatively small subset of patients (approximately 15, 8%, of 178 patients) fall into this category, and the toxicity of 3–4 cycles of cisplatin–5F-U is probably higher than that of limited-field radiation therapy or conservation surgery (particularly transoral laser resection).

An additional caveat is that the authors of this study are an extraordinarily talented group of surgeons specialising in conservation laryngeal surgery, so that the results of this study may be difficult to duplicate at other institutions. For comparison, the 5-year local control rates after radiation therapy alone for unselected patients with T1 and T2 glottic cancer at the University of Florida were T1A, 95%; T1B, 96%; T2A, 87%; and T2B, 76% [2]. Approximately two-thirds of patients with T3 glottic cancers were treated with radiation therapy alone with a 5-year local control rate of 63% [3].

INDUCTION CHEMOTHERAPY

The preponderance of the available data indicates that induction chemotherapy does not improve local-regional control and survival compared with radiation therapy and/or surgery [4–8]. Therefore, the potential role of induction chemotherapy is to select patients more likely to be cured by radiation therapy, with preservation of a functional larynx [9, 10]. The Department of Veterans Affairs Laryngeal Cancer Study Group randomised 332 patients with Stage III–IV glottic cancer (124 patients) and supraglottic cancer (208 patients) to Arm 1: 3 cycles of cisplatin–5-FU followed by radiation therapy in partial and complete responders and to surgery and postoperative irradiation for non-responders; or Arm 2, surgery and postoperative irradiation [9]. The larynx was preserved in approximately 64% of those randomised to receive induction chemotherapy; there was no survival difference between the arms at 9 years [11]. Additional evidence supporting this strategy may be extrapolated from the European Organization for Research and Treatment of Cancer (EORTC) trial where 202 patients with advanced squamous cell carcinoma of the pyriform sinus and aryepiglottic fold

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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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PII: S0959-8049(99)00130-6

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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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