HISTOLOGIC CHARACTERISTICS AND TUMOR SPREAD OF RECURRENT GLOTTIC CARCINOMA: ANALYSIS ON WHOLE-ORGAN SECTIONS AND COMPARISON WITH TUMOR SPREAD OF PRIMARY GLOTTIC CARCINOMAS

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Abstract: Background. The assessment of the precise tumor extent of recurrent glottic carcinomas is a challenge.

Methods. The histologic characteristics of 29 recurrent glottic carcinomas after radiation failures, initially classified as T1 and T2, were analyzed on whole-organ slices. The growth patterns of 21 recurrent prT3 and prT4 and 52 primary pT3 and pT4 carcinomas were compared.

Results. Fifteen of 29 (52%) recurrent carcinomas were understaged by imaging studies and endoscopy. Most recurrent carcinomas presented with multicentric tumor foci, whereas most primary carcinomas with a concentric tumor growth pattern (p < .05). Undifferentiated dissociated tumor cells were observed more often in the vicinity of recurrent tumor foci than of the primary tumor mass (p < .05).

Conclusion. Recurrent glottic carcinomas are often understaged and present with multiple tumor foci dispersed in different regions of the larynx. If voice-preserving salvage surgery is considered as a treatment option, these facts should be kept in mind.

Keywords: glottic carcinoma; recurrence; irradiation failure; tumor spread; voice-preserving surgery
spread of recurrent glottic carcinomas to laryngeal structures and to compare the growth pattern of prT3 and prT4 recurrent glottic carcinomas with the growth pattern of “de novo” pT3 and pT4 laryngeal carcinomas, involving the glottic level.

MATERIALS AND METHODS
Between October 1992 and April 2003, 168 T1 and T2 glottic carcinomas were treated with irradiation. All patients were clinically node-negative. Pretreatment work-up included microlaryngoscopy and CT or MRI in all patients. The tumors were irradiated in a narrow-field technique including only the appropriate lymph node levels in case of cT2. The daily radiation fraction ranged from 1.8 to 2.0 Gy and the total dose from 68 to 72 Gy. After completion of the radiation therapy, the patients were checked by clinical examination every 3 months for 2 years, every 4 months during the third year, and every 6 months in the subsequent 2 years. Recurrences occurred in 32 of 168 patients (19%). 14 of 85 patients with T1a disease (16.5%), 6 of 37 patients with T1b disease (16%), and 12 of 46 patients with T2 disease (26%). The work-up of recurrent carcinomas included a CT scan or MRI and an endoscopy with biopsies in all cases. The T2 carcinomas presented with a slight extension to the vocal cords, as described by Michaelis and Gregor.8 In selected cases, additional axial slices were cut at a thickness of 1 mm. At each level, at least 1 slice was processed for microscopic examination with hematoxylin-eosin staining. All lesions were staged according to the Union Internationale Contre le Cancer tumor-node-metastasis (TNM) classification and TNM supplement.9,10

Statistical significance was based on a p value less than .05.

RESULTS
Clinical T Classification Versus Pathologic T Classification of Recurrent Carcinomas. According to the indirect or fiberoptic laryngoscopy, CT scan or MRI findings, and microlaryngoscopic examination, 5 recurrent glottic carcinomas were classified as crT1, 6 as crT2, 13 as crT3, and 5 as crT4. With respect to pathologic assessment, 5 recurrent carcinomas were classified as prT1, 3 as prT2, 8 as prT3, and 13 as prT4. Three recurrent carcinomas were clinically overstaged, and 15 (52%) were understaged. The diagnostic accuracy was 11 of 29 (38%).

Growth Pattern of Recurrent Glottic Carcinoma. Table 1 shows laryngeal structures invaded by 8 prT1/T2, treated in 4 cases by classical voice-preserving salvage surgery and in 4 patients by a salvage total laryngectomy and by 21 prT3/T4 carcinomas, all treated by total salvage laryngectomy.

Comparison between 21 prT3/T4 Recurrent Carcinomas and 52 pT3/T4 “de novo” Carcinomas. The results of the histologic analysis of 21 recurrent and of 52 primary-surgery laryngectomy specimens are summarized in Table 1.

Tumor Growth Pattern. In the salvage-surgery and primary-surgery laryngectomy specimens, 4 of 21 (19%) and 40 of 52 (77%), respectively, presented with a concentric tumor growth (p ≤ .05). Eighteen recurrent tumors presented with multicentric foci, often surrounded by fibrosis (Figures 1A and 1B).

Cartilage Invasion (Figures 2A–2C). Neoplastic infiltration of the laryngeal framework was observed in 86% and 73% of salvage-surgery and primary-surgery laryngectomy specimens, respectively. The irradiated specimens showed a higher incidence of cricoid cartilage invasion than the primary-surgery specimens (62% vs 42%).

Subglottic Tumor Extension (Figures 3A–3C). Subglottic tumor extension was observed in 95% and 87%
of salvage-surgery and primary-surgery specimens, respectively. In 20 of 21 salvage surgery specimens, a subglottic tumor extension was present, although initially, a slight subglottic extension was observed in 3 T2 carcinomas only. In 2 recurrent carcinomas, even an infiltration of the trachea was observed (Figures 4A and 4B).

![Image](https://via.placeholder.com/150)

**FIGURE 1.** Tumor growth pattern of de novo and recurrent carcinoma. (A) De novo pT3 carcinoma presenting as a well-defined tumor mass. (B) Recurrent prT3 carcinoma presenting with numerous tumor foci in fibrous tissue (arrows). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

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### Table 1. Spread of laryngeal carcinoma.

<table>
<thead>
<tr>
<th></th>
<th>Salvage laryngectomy specimens prT1/prT2 n = 8</th>
<th>Salvage laryngectomy specimens prT3/prT4 n = 21 (%)</th>
<th>Primary-surgery laryngectomy specimens pT3/pT4 n = 52 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preepiglottic space</td>
<td>0</td>
<td>6 (28)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Paraglottic space (supraglottic level)</td>
<td>1</td>
<td>12 (57)</td>
<td>24 (46)</td>
</tr>
<tr>
<td>Paraglottic space (glottic level)</td>
<td>1</td>
<td>15 (71)</td>
<td>36 (69)</td>
</tr>
<tr>
<td>Anterior commissure</td>
<td>4</td>
<td>19 (90)</td>
<td>40 (77)</td>
</tr>
<tr>
<td>Posterior commissure</td>
<td>0</td>
<td>10 (48)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Subglottic region</td>
<td>2</td>
<td>20 (95)</td>
<td>45 (87)</td>
</tr>
<tr>
<td>Laryngeal framework</td>
<td>0</td>
<td>18 (86)</td>
<td>38 (73)</td>
</tr>
<tr>
<td>Thyroid cartilage</td>
<td>0</td>
<td>15 (71)</td>
<td>26 (50)</td>
</tr>
<tr>
<td>Cricoid cartilage</td>
<td>0</td>
<td>13 (62)</td>
<td>22 (42)</td>
</tr>
<tr>
<td>Arytenoid cartilage</td>
<td>0</td>
<td>11 (52)</td>
<td>18 (35)</td>
</tr>
<tr>
<td>Cricothyroid joint</td>
<td>0</td>
<td>8 (38)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Intrinsic laryngeal muscles</td>
<td>3</td>
<td>19 (90)</td>
<td>51 (98)</td>
</tr>
<tr>
<td>Contralateral tumor extension</td>
<td>4</td>
<td>18 (86)</td>
<td>37 (71)</td>
</tr>
<tr>
<td>Extralaryngeal tumor extension</td>
<td>0</td>
<td>13 (62)</td>
<td>28 (54)</td>
</tr>
<tr>
<td>Lymphangiosis</td>
<td>0</td>
<td>4 (19)</td>
<td>17 (33)</td>
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<tr>
<td>Hemangiosis</td>
<td>1</td>
<td>1 (5)</td>
<td>10 (19)</td>
</tr>
<tr>
<td>Perineural infiltration</td>
<td>2</td>
<td>17 (81)</td>
<td>28 (54)</td>
</tr>
<tr>
<td>Dissociated tumor cells</td>
<td>2</td>
<td>16 (76)</td>
<td>12 (33)</td>
</tr>
<tr>
<td>Multicentric tumor foci</td>
<td>4</td>
<td>17 (81)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>Mean horizontal tumor extension, mm</td>
<td>17</td>
<td>29.8</td>
<td>27.9</td>
</tr>
<tr>
<td>Range, mm</td>
<td>17/46</td>
<td>10/45</td>
<td></td>
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</tbody>
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Contralateral Tumor Extension (Figures 2A, 3A, 3B). In 86% and 71% of salvage and primary-surgery laryngectomy specimens, respectively, a contralateral tumor extension was observed \((p < 0.05)\). Six of 21 recurrent (28%) and 7 of 52 (13%) primary carcinomas presented contralateral tumor spread at the anterior part (anterior commissure, preepiglottic space) as well as at the posterior part (post-

**FIGURE 2.** Pattern of cartilage infiltration of de novo and recurrent carcinoma. (A) A well-demarcated cartilage zone is infiltrated and destroyed by a de novo carcinoma. (B) The recurrent carcinoma, initially a T2 glottic carcinoma, infiltrates the ossified cartilage by numerous tumor foci. (C) High-power view (rectangle Figure 2B) of multiple tumor foci within the ossified cartilage (arrow) \((\times 2.5)\). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

**FIGURE 3.** Subglottic tumor extension. (A) Well-defined subglottic tumor extension of a de novo carcinoma. (B) Multiple tumor foci of a recurrent T1a carcinoma. (C) High-power view (rectangle Figure 3B) with tumor foci (arrows) within fibrous tissue \((\times 2.5)\). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
terior commissure, interarytenoid muscle) of the larynx.

Vertical and Horizontal Tumor Extension (Figures 4A–4D). Fifteen of 21 (71%)
recurrent carcinomas, 8 of which were initially confined exclusively to the glottic level, presented with tumor extension to the supraglottic and/or subglottic levels. The mean extent of the greatest horizontal tumor extension was 2 mm greater in the salvage surgery specimens compared with the primary-surgery specimens (27.9 mm vs 29.8 mm).

Dissociated Tumor Cells (see Figure 5). In 76% and 23% of salvage and primary-surgery specimens, respectively ($p < .05$), dissociated and isolated tumor cells were observed in the vicinity of the tumor foci of recurrent carcinomas or of the concentric growing primary tumors.

Extralaryngeal Tumor Spread (see Figure 6). Extralaryngeal tumor spread was observed in 62% and 54% of recurrent-surgery and primary-surgery specimens, respectively. Interestingly, in some cases of recurrent carcinomas, the extralaryngeal tumor consists exclusively of a few isolated tumor foci.

Perineural Spread (see Figure 7). Perineural tumor spread was observed in 81% and 54% of recurrent surgery and primary-surgery specimens, respec-

FIGURE 4. Tumor recurrence with supraglottic, subglottic, and tracheal infiltration of a T2 carcinoma, initially confined exclusively to the glottic level. (A) Tumor foci in the tracheal mucosa at the level of the second tracheal ring (rectangle). (B) High-power view (rectangle Figure 4A) with submucosal tumor nests (arrows) ($\times 2.5$). (C) Supraglottic tumor extension with tumor nest near the epiglottic cartilage (rectangle). (D) High-power view (rectangle Figure 4C) of tumor nest in the fat tissue (arrows) ($\times 2.5$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIGURE 5. Dissociated and isolated tumor cells (arrows) in the subglottic area of an initially T2 glottic carcinoma with a slight extension to the ventricle ($\times 20$). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
tively. In the recurrent carcinomas in contrast to the primary carcinomas, not only a few nerves but most nerves were affected by tumor.

DISCUSSION

Clinical T Versus Pathologic T Classification of Recurrent Carcinomas. The assessment of the exact tumor extension of recurrent laryngeal carcinomas may be difficult because of the residual inflammatory or the functional changes associated with radiation therapy. Furthermore, tumor recurrence may be localized submucosally—invisible during endoscopy—or may consist of microscopic tumor foci, undetectable by imaging studies, both facts being possible reasons as to why recurrent glottic carcinomas are not rarely detected in an advanced pathologic tumor stage. Many authors observed that the recurrent T classification was more advanced than the initial T classification in 50% to 60%.1,2,11 In most papers dealing with laryngeal tumor recurrences, the pathologic T classification of tumor recurrence is not mentioned2,3,5,6,11–13 because, in many centers, laryngectomy specimens are not analyzed on whole-organ slices. Furthermore, we observed in our study on whole-organ sections that recurrent tumors are often understaged by endoscopy and imaging studies. Whereas prospective studies comparing imaging and endoscopic findings of primary laryngeal carcinomas with histologic tumor extension on whole-organ sections have been performed,14,15 such studies regarding recurrent laryngeal carcinomas are lacking.

Growth Pattern of Recurrent Glottic Carcinoma. Tumor extension into the cartilage, the subglottic region, and contralateral tumor spread preclude classical voice-preserving laryngeal surgery. In our series of 29 salvage surgery specimens, 52% and 45% presented with thyroid or cricoid cartilage infiltration, respectively, and 76% with subglottic tumor extension (Figures 3B and 3C). Furthermore, an extralaryngeal tumor spread was observed in 45% of the 29 initially intralaryngeal glottic T1 and T2 carcinomas (see Figure 6). Interestingly, in 6 laryngectomy specimens—despite the advanced pathologic recurrent tumor stage—the paraglottic space at the glottic level was not infiltrated: in 3 of them, the thyroid cartilage was slightly infiltrated at the anterior commissure (prT3); in 1 laryngectomy specimen with an anterior localized glotto-supraglottic tumor recurrence, the preepiglottic space was infiltrated (prT3); in 2 further specimens, the recurrent tumor was classified as prT3, according to the TNM Supplement 1993,10 as “histological tumor invasion of more than 5 mm corresponds to impaired vocal cord mobility or vocal cord fixation.” The most striking observation in our study was the presence of multicentric tumor foci dispersed in different parts of the larynx, even in extralaryngeal sites (see Figure 6). Brandenberg et al16 similarly observed multicentric tumor foci and stated, “the fibrosis (within it multicentric tumor foci are observed) corresponded to the clinically described sites of the tumors before radiotherapy.” This interpretation does not correspond to our observations as in our series 18 carcinomas were initially exclusively confined to

FIGURE 6. Extralaryngeal tumor spread of a recurrent T2 glottic carcinoma; perivascular tumor foci (arrowhead); tumor nests in fibrous tissue (arrow) (×2.5). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIGURE 7. Recurrent carcinoma with extensive perineural tumor infiltration (×2.5). [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
the glottic level and the other 11 presented only with a minimal extension to the ventricle (n = 8) or subglottic region (n = 3). Brandenburg et al16 presumed that tumors follow mucous glands and blood vessels into areas of the larynx unaffected by tumor. In 66% of recurrent carcinomas in our series, we observed a strongly marked perineural infiltration, evoking the hypothesis that tumors also grow along nerves in areas previously unaffected by tumor (see Figure 7).

**Comparison between prT3/T4 (Initially T1 and T2 Glottic Carcinomas) and pT3/T4 Glottic Carcinomas.** The most obvious differences in growth pattern between the recurrent and primary glottic carcinoma were as follows: the multifocality of tumor nests in recurrent tumors versus the concentric growth pattern in primary carcinomas (p = .0001) (Figures 1A and 1B); the high percentage of undifferentiated dissociated tumors cells in the recurrent carcinomas (73% vs 23%; p = .0007) (see Figure 5); the high percentage of perineural infiltration in recurrent tumors (82% vs 54%; p = .053) (see Figure 7); the high ratio of cricoid cartilage infiltration in recurrent tumors (59% vs 42%); and the high percentage of contralateral tumor spread (86% vs 71%). In addition, tumor infiltration of the cricoarytenoid joint and extralaryngeal tumor spread is more often observed in salvage-surgery than in primary-surgery specimens. Furthermore, the mean measure of the greatest horizontal tumor extension is greater in recurrent carcinomas (29.8 mm vs 27.9 mm). To avoid local failures after voice-preserving salvage surgery, the following observations should be kept in mind when voice-preserving salvage surgery is considered: recurrent tumors are often understaged by imaging studies and endoscopy; the histologic growth pattern of recurrent laryngeal carcinomas is different from the growth pattern of the “de novo” carcinomas (multifocal tumor nests in recurrent carcinoma versus concentrical growth pattern in “de novo” carcinomas).

**REFERENCES**