Prognostic Factors of Glottic Carcinomas Treated with Radiation Therapy: Value of The Adjacent Sign on Radiological Examinations in The Sixth Edition of The UICC TNM Staging System

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Purpose

To evaluate the predictive value of the adjacent sign, the tumor adjacent to the thyroid cartilage on radiological examinations, in the new 6th edition of the UICC staging system of glottic carcinoma.
Background

1. *TNM staging system (UICC 6th edition)*

T3-stage glottic carcinoma includes paraglottic space invasion and/or minor thyroid cartilage erosion in addition to the vocal cord fixation in the 5th edition.

2. *Paraglottic space/Thyroid cartilage invasion*

Minor invasion is difficult to diagnose radiologically, and not a significant predictor for local recurrence following definitive RT.

3. *Adjacent sign*

The adjacent sign representing “deep” paraglottic space invasion with/without minor thyroid cartilage erosion should be considered as the radiological parameter identifying a T3 lesion.
TNM Classification (UICC 6th edition)

**T1**  Tumour limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
  - **T1a**  Tumour limited to one vocal cord
  - **T1b**  Tumour involves both vocal cords

**T2**  Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility

**T3**  Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or with minor thyroid cartilage erosion (e.g., inner cortex)

**T4a**  Tumour invades through the thyroid cartilage, or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus.

**T4b**  Tumour invades prevertebral space, mediastinal structures, or encases carotid artery
Paraglottic Space Invasion

*CT data (University of Florida College of Medicine)*
Paraglottic invasion is a significant predictor for the local control of T3-, but not T2 glottic carcinoma treated with definitive RT.


*CT data (Hermans R, et al.)*
The degree of paraglottic space invasion is an independent predictor for local recurrence of glottic carcinoma treated with RT. The local failure rates for tumors with no-, one-third, two-thirds, and whole paraglottic space invasion were 15% (10 of 66), 13% (2 of 15), 25% (4 of 16), and 55% (12 of 22), respectively.

Radiotherapy and Oncology 50:39-46, 1999
Thyroid Cartilage Invasion

**CT data (University of Florida College of Medicine)**

Single-cartilage sclerosis is a significant predictor in high-volume, but not low-volume tumors treated with definitive RT.

*AJ NR Am J Neuroradiol 16:655-662, 1995*
*Int J Radiat Oncol Biol Phys 37:1011-1021, 1997*

**MR data (Castelijns et al.)**

Abnormal signal patterns of cartilages indicate a poor prognosis in large (>5 cm³), but not small (<5 cm³) tumors treated with RT.

*Radiology 198:151-155, 1996*
Adjacent sign

Murakami R, et al.

CT and MR studies suggested that patients with a tumor adjacent to the thyroid cartilage had an increased risk of local failure following RT.

Acta Radiol 41:38-44, 2000
A 57-year-old man with T2 glottic carcinoma classified with the UICC 5th edition. Dynamic MRI (TR/TE = 583/14) shows the tumor to be adjacent to the thyroid cartilage. This lesion was classified as T3 stage in the UICC 6th ed.
Methods and Materials

• Between 1989 and 1998

• 193 patients with T1-2 N0 glottic SCC (UICC 5th ed.) were treated with definitive RT.

• 130 patients evaluated with CT and/or MRI.
  • Male: 127, Female: 3
  • Age: 38-93 y.o. (mean: 68 y.o.)
  • Follow-up time: 10-175 months (mean: 75 months)
Definitive Radiation Therapy

- RT for T1-T2 stage (UICC 5th ed.)
  → Salvage surgery for local failures

- 3 MV X-ray using opposed lateral fields
  - Field size: 5-6 cm
  - Fraction dose: 1.8-2.2 Gy
  - Total dose
    - T1a: 60-66 Gy
    - T1b, T2: 64-70 Gy
## Results 1

### T Staging

<table>
<thead>
<tr>
<th>UICC 5th ed.</th>
<th>UICC 6th ed.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T1a:</strong> 47 (3)</td>
<td><strong>T1a:</strong> 44</td>
</tr>
<tr>
<td><strong>T1b:</strong> 34 (5)</td>
<td><strong>T1b:</strong> 29</td>
</tr>
<tr>
<td><strong>T2:</strong> 49 (22)</td>
<td><strong>T2:</strong> 27</td>
</tr>
<tr>
<td><strong>T3:</strong> 30 (30)</td>
<td><strong>T3:</strong> 30 (30)</td>
</tr>
</tbody>
</table>

(adjacent sign positive)

* Tumors with the adjacent sign were retrospectively classified as T3 stage in the UICC 6th edition.
Results 2

Local control

30 of the 130 patients were recorded as local failures.

• The 5-year local control rate following RT: 76%

Treatments for 30 local failures

• Laser therapy 5
• Hemilaryngectomy 5
• Total laryngectomy 16
• Conservative therapy 4

• The 5-year laryngeal preservation rate: 84%
Results 3

Survival

39 of the 130 patients died.

- The 5-year overall survival rate: 75%

Cause of death

- Glottic carcinoma: 7
- Second primary tumor: 18
- Intercurrent disease: 14

- The 5-year cause-specific survival rate: 94%
Results 4

Prognostic factors for local control

Univariate analysis

- UICC 5th ed.
- UICC 6th ed.
- Supraglottic extension
- Subglottic extension
- Total dose
- Fraction size
- Overall treatment time

Multivariate analysis

- UICC 6th ed.
### Prognostic factors

<table>
<thead>
<tr>
<th>Category</th>
<th>No. of patients</th>
<th>5-year Univariate local analysis (p-value)</th>
<th>Multivariate analysis (p-value)</th>
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<td>Clinical Characteristics</td>
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<tr>
<td>Age</td>
<td>≤69 / ≥70</td>
<td>72 / 58</td>
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<td>UICC 5th ed.</td>
<td>T1 / T2</td>
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<td>.0033</td>
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<tr>
<td>UICC 6th ed.</td>
<td>T1,2 / T3</td>
<td>100 / 30</td>
<td>&lt;.0001</td>
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<td>Tumor shape</td>
<td>exophytic / infiltrative</td>
<td>85 / 45</td>
<td>.4714</td>
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<td>Vocal cord mobility</td>
<td>good / limited</td>
<td>126 / 4</td>
<td>.8779</td>
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<tr>
<td>Anterior commissure</td>
<td>intact / extent</td>
<td>71 / 59</td>
<td>.6682</td>
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<td>Supraglottic</td>
<td>intact / extent</td>
<td>87 / 43</td>
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<td>Subglottic</td>
<td>intact / extent</td>
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<td>Treatment Characteristics</td>
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<td>Total dose</td>
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<td>Fraction size</td>
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<td>Overall treatment time</td>
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<td>Interruption</td>
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<td>Total</td>
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Local control rate curves using the UICC 6th ed.

5-year local control
- T1a (n=44): 91%
- T1b (n=29): 86%
- T2 (n=27): 83%
- T3 (n=30): 37%
## Results 5

### Treatment effects

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Local control rate (%)</th>
<th>Laryngeal preservation rate (%)</th>
<th>Cause-specific survival rate (%)</th>
<th>Overall survival rate (%)</th>
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<td>T3</td>
<td>30 (30)</td>
<td>37</td>
<td>47</td>
<td>75</td>
<td>54</td>
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</tbody>
</table>

(adjacent sign positive)
Results 6

Based on UICC 6th ed. (T3 vs. T1-2)

- Local control: 37% vs. 87% (p<0.0001)
- Laryngeal preservation: 47% vs. 95% (p<0.0001)
- Cause-specific survival: 75% vs. 99% (p<0.0001)
- Overall survival: 54% vs. 81% (p=0.0180)
Conclusion

1. Factor analysis confirmed the adjacent sign as an independent prognostic factor.

2. The UICC 6th edition appears to successfully identify the high-risk group as T3 stage.