Evidence Summary 5-4 EDUCATION AND INFORMATION 2011

Optimum Radiation Fractionation for T1 N0 Glottic (Vocal Cord) Carcinoma

A Quality Initiative of the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Evidence Summary (ES) 5-4 was reviewed and put in the Education and Information section in September 2011. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

The reviewed report consists of:
1. Guideline Report Overview
2. Summary
3. Full Report

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Head and Neck Cancer Disease Site Group page at:
https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/head-neck-ebs/

Release Date: April 3, 2012

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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Evidence Summary 5-4 EDUCATION AND INFORMATION 2011

Optimum Radiation Fractionation for T1 N0 Glottic (Vocal Cord) Carcinoma

Guideline Report History

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<td>April 2012</td>
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Optimum Radiation Fractionation for T1 N0 Glottic (Vocal Cord) Carcinoma

Guideline Review Summary

Review Date: September 2011

The 1998 evidence summary is

ARCHIVED

This means that the document will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW
Evidence-based Series History

This evidence summary report was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 1998. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Summary and Full Report in this version are the same as 1998 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is completed with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore no update search was conducted. The 1998 Evidence Summary report on Optimum Radiation Fractionation for T1 N0 Glottic (Vocal Cord) Carcinoma has been ARCHIVED.
Update strategy outcomes definitions.

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED.”

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.
Evidence Summary Report 5-4

Optimum Radiation Fractionation for T1 N0 Glottic (Vocal Cord) Carcinoma

D.I. Hodson, S. Archibald, G.P. Browman, M. Johnston, C. Cripps, J. Davidson, and members of the Head and Neck Cancer Disease Site Group

SUMMARY

Question
What is the optimum dose and fractionation schedule for the radiation treatment of patients with T1 N0 glottic (vocal cord) carcinoma?

Target Population
This evidence summary applies to adult patients with T1 NO glottic (vocal cord) carcinoma.

Methods
Entries to MEDLINE (1980 through July 2004), CANCERLIT (1980 through July 2001), EMBASE (through 2004), the Cochrane Library (Issue 2, 2004), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology (1995-2004), the American Society for Therapeutic Radiology and Oncology (1999-2004), and the European Society for Medical Oncology (2000) were systematically searched for evidence relevant to this evidence summary report. Article bibliographies and personal files were also searched to July 2004.

Evidence was selected and reviewed by one member of the Practice Guidelines Initiative’s Head and Neck Cancer Disease Site Group and methodologists. This evidence summary has been reviewed and approved by the Head and Neck Cancer Disease Site Group Disease, which is comprised of medical and radiation oncologists, surgeons, and epidemiologists.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report and evidence summary. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.
Key Evidence
The quality of evidence is insufficient to comment on the superiority of any one of the fractionation schedules described, with respect to either disease control or toxicity. Control rates, found in 30 case series, ranged from 62% to 100%. One study reported excessive toxicity with fractions of 333 cGy three times weekly to 60 Gy in six weeks using a single field.

Conclusions
The quality of the current evidence concerning the optimum dose and fractionation schedule for radiotherapy treatment of T1 N0 cancer of the glottic larynx is poor. The vast majority of clinical papers are retrospective reviews of case series from single institutions. The evidence available does not allow a firm clinical recommendation to be made.

Accepted schedules are based on the delivery of a radical radiation dose with a clinically acceptable complication rate. There is no evidence for the superiority of any one treatment schedule. A four-week course of treatment appears to be safe and effective.

For further information about this practice guideline, please contact: Dr. Ralph Gilbert, Chair, Head and Neck Cancer Disease Site Group, Princess Margaret Hospital, 610 University Avenue, Toronto, Ontario, Canada M5G 2M9 Tel: 416-946-2822 Fax: 416-946-2300 E-mail: ralph.gilbert@uhn.on.ca

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit www.cancercare.on.ca/ for all additional Practice Guidelines Initiative reports.
PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.¹

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822  Fax: 905-526-6775  E-mail: ccopgi@mcmaster.ca

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Disclaimer
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I. QUESTION
What is the optimum dose and fractionation schedule for the radiation treatment of patients with T1 N0 glottic (vocal cord) carcinoma?

II. CHOICE OF TOPIC AND RATIONALE
T1 N0 glottic carcinoma is a relatively common and radiocurable lesion exemplifying the unique organ sparing advantages of successful radiation therapy. Excellent control has been reported following external beam radiation. The treatment volumes required are relatively small which allows radical radiotherapy doses to be delivered with minimal acute and chronic toxicity.

Radiation therapy is generally accepted as the treatment of choice for the majority of T1 N0 glottic cancers. However, there is wide variation in the fractionation schedules of the treatment courses used. Priestman et al (1) conducted a mailed survey of 165 consultants in Great Britain, asking about the fractionation they used for the radiation treatment of T1 N0 glottic cancer. Twenty-one percent reported using 60 Gy in six weeks; 8%, 55 Gy in four weeks; 8%, 55 Gy in 16 daily treatments; and the remaining 63% used 44 different treatment schedules.

A survey in 1996 of the eight Cancer Care Ontario Regional Cancer Centres showed that six different schedules were being used for the treatment of T1 N0 glottic carcinoma (Table 1). In three centres, two different regimens were used. Warde et al (2) reported that 97% of patients received 5000 cGy in 20 fractions over four weeks at the Princess Margaret Hospital in Toronto.

In November 1997, the Head and Neck Cancer Disease Site Group (DSG) completed a guideline-in-progress report (a systematic review of the evidence plus draft recommendations) on this topic and sent it to 27 practitioners in Ontario for feedback. Fifty six percent of the practitioners returned their feedback questionnaires and of these, only 40% approved of the draft recommendations serving as recommendations as a practice guideline. The main reason for the other 60% objecting to the adoption of the draft recommendations was the lack of high-quality evidence to recommend one treatment regimen over another. Based on the practitioner feedback, there was general consensus among the Head and Neck Cancer DSG members to reformat the guideline-in-progress report as an evidence summary, i.e., as a systematic review of the evidence without treatment recommendations.

Table 1. T1 N0 glottic cancer: results of survey of the 8 Ontario regional cancer centres, 1996.

<table>
<thead>
<tr>
<th>Course (Total dose [cGy]/number of fractions)</th>
<th>*Number Of Centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000/20**</td>
<td>3</td>
</tr>
<tr>
<td>5250/20</td>
<td>1</td>
</tr>
<tr>
<td>5500/25</td>
<td>1</td>
</tr>
<tr>
<td>6000/25</td>
<td>1</td>
</tr>
<tr>
<td>6100/25</td>
<td>1</td>
</tr>
<tr>
<td>6600/33</td>
<td>2</td>
</tr>
</tbody>
</table>

* In 3 centres, more than one fractionation course was used.
** Warde et al reported on treatment results at the Princess Margaret Hospital Cancer Centre, where 97% of patients were treated with 5000 cGy in 20 fractions over 4 weeks (2).
III. METHODS

Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario’s Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle\(^2\). Evidence was selected and reviewed by one member of the PGI’s Head and Neck Cancer DSG and methodologists. Members of the Head and Neck Cancer DSG disclosed potential conflict of interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on optimum radiation fractionation for T1 NO glottic (vocal cord) carcinoma, developed through systematic reviews, evidence synthesis and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. This precludes the development of definitive recommendations and instead, opinions of the DSG are offered. The report is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The PGI has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Evidence Summary History


Literature Search Strategy

MEDLINE and CANCERLIT searches of the English language literature were performed for the period from 1980 to October 1998. “Glottis” (Medical subject heading [MeSH]) and “neoplasms” (MeSH) or “laryngeal neoplasms” (MeSH) were combined with “radiotherapy” (MeSH) and “surgery” (MeSH) and the following phrases used as text words: “irradiat:,” “surgery”. These terms were then combined with the search terms for the following study designs: longitudinal studies, retrospective studies, comparative studies, clinical trials, meta-analyses. The search was limited to English language articles. PREMEDLINE was searched in October 1998 for recently published articles, using the textwords “glottic,” “T1” and “radiotherapy”. The citation lists of all retrieved articles were reviewed to identify further studies.

Update

The original literature search has been updated using MEDLINE (through March 2005), EMBASE (through March 2005), the Cochrane Library (Issue 1, 2005), the Physician Data Query database, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse, as well as abstracts published in the proceedings of the meetings of the American Society of Clinical Oncology (1995-2005) and the American Society for Therapeutic Radiology and Oncology (2000-2004). Article bibliographies and personal files were also searched to March 2005 for evidence relevant to this practice guideline report.

Inclusion Criteria
Studies were selected for detailed analysis if data pertaining to radiation dose and fractionation, and local control rates could be abstracted.

Update
A substantial number of eligible studies continue to be reported in the literature, but additional results from case series will not enable the Head and Neck Cancer DSG to make firm clinical recommendations. For this reason, the decision was made that, until results from randomized clinical trials become available, only reports from Canadian centres would be added to this report during updates of the literature search.

Exclusion Criteria
Articles were excluded if data specific to T1 N0 glottic cancer could not be obtained.

Synthesizing the Evidence
In order to get overall, precise estimates of tumour control rates, results were pooled for studies with the same or similar doses of radiation per fraction. An average control rate, weighted by study sample size, was calculated for each dose per fraction.

IV. RESULTS
Literature Search Results
Thirty-one papers reporting treatment results for T1 N0 glottic cancer were eligible for detailed analysis. The quality of the retrieved evidence was poor. One randomized trial (3) was included, but this study addressed the issue of optimum field size and not the dose level or fractionation of treatment. One comparative cohort study using a historical cohort control was found (4). This study concluded that total dose was a significant factor for the control of T1a glottic disease. However, the lower dose range used for the comparison was 20 to 40 Gy over two to four weeks and is not relevant to current practice. This left 30 papers that reported evidence from case series (2,3,5-32).

Treatment Results
Tables 2 to 6 provide a summary of 30 case series organized by dose per fraction of the treatment course. Rates of local control by radiation alone, successful surgical salvage, and chronic complications are tabulated.

Tumour control rates were pooled for the data presented in Tables 2 to 4. Four studies, evaluating doses less than 200 cGy per fraction in a total of 117 patients, had an average control rate of 73% (95% confidence interval (CI), 65% to 81%) (5-8). The largest group of studies reported control rates with a dose per fraction of 200 cGy (3,7,9-19). Pooling results from these 13 cases series, involving a total of 1442 patients, gave an average control rate of 88% (95% CI, 86% to 90%). The average tumour control rate was also 88% (95% CI, 86.5% to 90%) for 11 studies with a total of 1866 patients treated with doses per fraction ranging from 210 to 290 cGy (2,5,15,19-26). There was considerable overlap among results for these three groups of studies, with the lowest and highest tumour control rates reported as: 62% and 79% for doses per fraction less than 200 cGy, 66% and 97% for 200 cGy, and 63% and 96% for doses per fraction greater than 200 cGy but less than 300 cGy. Two papers reported results for doses greater than 300 cGy given three times per week; Kok reported a tumour control rate of 71% with 320 or 385 cGy (5), and Randall et al reported a tumour control rate of 92% with 333 cGy (27). Table 6 lists results from seven series of patients treated with a broad range of doses per fraction (6,8,28-32). Tumour control rates for these varied from 80 to 100%.

The presence or absence of an influence of dose per fraction on local control remains unresolved. Two univariate analyses of retrospective data found lower control rates with doses per fraction of less than 200 cGy (6,7). Yu et al (19) reported that fraction size was the only significant prognostic factor for local control in their multivariate analysis and concluded that daily fractions
larger than 200 cGy were associated with better local control than fractions of 200 cGy. However, multivariate analyses by Rudoltz et al (8) and Krawczyk et al (31) concluded that elapsed days of treatment was the only factor which significantly affected local control and survival. All fractionation courses currently given in Ontario use a dose per fraction of 200 cGy or more, with two of eight centres using 200 cGy.

Similarly, the literature does not resolve the issue of total dose or time over which the radiotherapy should be given. A review of the British Institute of Radiology trial results by Rezvani et al (33), addressing radiobiologic concepts, suggested that the duration of treatment delivery for control of T1 N0 laryngeal tumours is significantly different from that for T2 and T3 tumours. The authors concluded that, “It is possible that T1 tumours are so controllable by radiotherapy that the longer overall treatment times were of no detriment” (33). Taylor et al (34) found no relationship between disease control rate and dose and time factors for T1 N0 glottic lesions treated with radiation in the range of 35 to 66 Gy over 28 to 50 days. Pellitteri et al (16) reported a 93% control rate using 6000 cGy in 30 fractions. Warde et al (2) have reported a local control rate of 90% with minimal toxicity using 5000 cGy in 20 fractions.

### Table 2. Summary of results for radiation therapy of T1 N0 glottic cancer: dose/fraction less than 200 cGy.

<table>
<thead>
<tr>
<th>Author (Reference), Year of Publication</th>
<th>Number of Patients</th>
<th>Dose/Fraction (cGy)</th>
<th>Total Dose (cGy)</th>
<th>Control by Radiotherapy</th>
<th>Successful Surgical Salvage</th>
<th>Incidence of Late Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kok (5)* 1971</td>
<td>17</td>
<td>175, 190</td>
<td>6300</td>
<td>76%</td>
<td>not reported</td>
<td>none</td>
</tr>
<tr>
<td>Schwaibold et al (6)* 1988</td>
<td>21</td>
<td>180</td>
<td>6660</td>
<td>67%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Kim et al (7)* 1992</td>
<td>58</td>
<td>180</td>
<td>6517</td>
<td>79%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Rudoltz et al (8)* 1993</td>
<td>21</td>
<td>&lt;200</td>
<td>6480</td>
<td>62%</td>
<td>not reported for the &lt;200 cGy group</td>
<td>none</td>
</tr>
</tbody>
</table>

*Data for additional dose group(s) from this study appear in other tables.*
Table 3. Summary of results for radiation therapy of T1 N0 glottic cancer: dose/fraction of 200 cGy.

<table>
<thead>
<tr>
<th>Author (Reference) Year of Publication</th>
<th>Number of Patients</th>
<th>Dose/Fraction (cGy)</th>
<th>Total Dose (cGy)</th>
<th>Control by Radiotherapy</th>
<th>Successful Surgical Salvage</th>
<th>Incidence of Late Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang (9) 1974</td>
<td>311</td>
<td>200</td>
<td>6500-7000</td>
<td>92%</td>
<td>not reported for T1 group</td>
<td>2.6% necrosis of the larynx (T1-T4)</td>
</tr>
<tr>
<td>Mills (10) 1979</td>
<td>49</td>
<td>200</td>
<td>5500-7000</td>
<td>89%</td>
<td>10/11</td>
<td>none</td>
</tr>
<tr>
<td>van den Bogaert et al (11) 1982</td>
<td>138</td>
<td>200</td>
<td>4000-7000</td>
<td>83%</td>
<td>19/22</td>
<td>not reported</td>
</tr>
<tr>
<td>Mantravadi et al (12) 1983</td>
<td>73</td>
<td>200</td>
<td>5000-7100</td>
<td>82%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Kaplan et al (13) 1984</td>
<td>166</td>
<td>200</td>
<td>6000-6500</td>
<td>88%</td>
<td>14/15</td>
<td>none</td>
</tr>
<tr>
<td>Sinha (14) 1987</td>
<td>74</td>
<td>200</td>
<td>6000-7000</td>
<td>85%</td>
<td>6/9</td>
<td>none</td>
</tr>
<tr>
<td>Lusinchi et al (15) 1989</td>
<td>140</td>
<td>200</td>
<td>6000-7200 (90% rec’d 6500 cGy)</td>
<td>79%</td>
<td>not reported for 200 cGy group</td>
<td>not reported for 200 cGy (1% permanent tracheostomy overall)</td>
</tr>
<tr>
<td>Teshima et al (3) 1990</td>
<td>87</td>
<td>200</td>
<td>6000</td>
<td>94%</td>
<td>5/5</td>
<td>none</td>
</tr>
<tr>
<td>Pellitteri et al (16), 1991</td>
<td>113</td>
<td>200</td>
<td>6000</td>
<td>93%</td>
<td>6/8</td>
<td>1% temporary tracheostomy</td>
</tr>
<tr>
<td>Terhaard et al (17), 1991</td>
<td>194</td>
<td>200</td>
<td>5800-6800</td>
<td>91%</td>
<td>13/19</td>
<td>0.9% temporary tracheostomy</td>
</tr>
<tr>
<td>Kim et al (7)*, 1992</td>
<td>27</td>
<td>200</td>
<td>6390</td>
<td>96%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Morris et al (18), 1994</td>
<td>38</td>
<td>200</td>
<td>6600</td>
<td>97%</td>
<td>10/10</td>
<td>none</td>
</tr>
<tr>
<td>Yu et al (19)*, 1997</td>
<td>32</td>
<td>200</td>
<td>6600</td>
<td>66%</td>
<td>not reported for 200 cGy group</td>
<td>none</td>
</tr>
</tbody>
</table>

* Data for additional dose group(s) from this study appear in other tables.
Table 4. Summary of results for radiation therapy of T1 N0 glottic cancer: dose/fraction greater than 200 cGy and less than 300 cGy.

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Year of Publication</th>
<th>Number of Patients</th>
<th>Dose/Fraction (cGy)</th>
<th>Total Dose (cGy)</th>
<th>Control by Radiotherapy</th>
<th>Successful Surgical Salvage</th>
<th>Incidence of Late Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kok (5)* 1971</td>
<td></td>
<td>32</td>
<td>210 (5X weekly)</td>
<td>6300</td>
<td>63%</td>
<td>not reported</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>240-290 (3X weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horiot et al (20)</td>
<td>1972</td>
<td>281</td>
<td>275 (1959-61)</td>
<td>5500-7000</td>
<td>88%</td>
<td>29/33</td>
<td>275 cGy: 10% 212-215 cGy: 0.7% (edema or necrosis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>212-217 (after 1961)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fletcher et al (21)</td>
<td>1975</td>
<td>210</td>
<td>212-250</td>
<td>5000-7000</td>
<td>86%</td>
<td>26/29</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4X weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luk &amp; Castro (22)</td>
<td>1975</td>
<td>43</td>
<td>230 (4X weekly)</td>
<td>6000</td>
<td>80%</td>
<td>not reported</td>
<td>none</td>
</tr>
<tr>
<td>Harwood et al (23)</td>
<td>1979</td>
<td>378</td>
<td>211-229</td>
<td>5500</td>
<td>86%</td>
<td>31/48</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(4X weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mendenhall et al</td>
<td>1979</td>
<td>171</td>
<td>210-225</td>
<td>5600-6700</td>
<td>93%</td>
<td>7/12</td>
<td>0.5% serious complications</td>
</tr>
<tr>
<td>(24) 1988</td>
<td></td>
<td></td>
<td>(4X weekly)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelly et al (25)</td>
<td>1989</td>
<td>95</td>
<td>240</td>
<td>6000</td>
<td>94%</td>
<td>5/5</td>
<td>1% permanent tracheostomy</td>
</tr>
<tr>
<td>Lusinchi et al (15)</td>
<td>1989</td>
<td>42</td>
<td>250 (4X weekly)</td>
<td>6000-7200 (90% rec’d 6500 cGy)</td>
<td>83%</td>
<td>not reported for &gt;200 cGy group</td>
<td>not reported for &gt;200 cGy (1% permanent tracheostomy overall)</td>
</tr>
<tr>
<td>Fein et al (26)</td>
<td>1993</td>
<td>132</td>
<td>225</td>
<td>5400-6525</td>
<td>96%</td>
<td>4/6</td>
<td>0.8% temporary tracheostomy</td>
</tr>
<tr>
<td>Yu et al (19)*</td>
<td>1997</td>
<td>32</td>
<td>200</td>
<td>6600</td>
<td>66%</td>
<td>not reported for &gt;200 cGy group</td>
<td>none</td>
</tr>
<tr>
<td>Warde et al (2)</td>
<td>1998</td>
<td>449</td>
<td>250</td>
<td>5000</td>
<td>90%†</td>
<td>not reported</td>
<td>not reported</td>
</tr>
</tbody>
</table>

* Data for additional dose group(s) from this study appear in other tables.  
† Data obtained from earlier abstract presented at the 4th International Conference on Head and Neck Cancer in Toronto, 1996.
Table 5. Summary of results for radiation therapy of T1 N0 glottic cancer: dose/fraction > 300 cGy.

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Year of Publication</th>
<th>Number of Patients</th>
<th>Dose/Fraction (cGy)</th>
<th>Total Dose (cGy)</th>
<th>Control by Radiotherapy</th>
<th>Successful Surgical Salvage</th>
<th>Incidence of Late Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kok (5)* 1971</td>
<td></td>
<td>14</td>
<td>320, 385 (3X weekly)</td>
<td>6300</td>
<td>71%</td>
<td>not reported</td>
<td>none</td>
</tr>
<tr>
<td>Randall et al (27)</td>
<td>1991</td>
<td>71</td>
<td>333 (3X weekly)</td>
<td>6000</td>
<td>92%</td>
<td>5/6</td>
<td>none</td>
</tr>
</tbody>
</table>

*Data for additional dose group(s) from this study appear in other tables.

Table 6. Summary of results for radiation therapy of T1 N0 glottic cancer: range of doses/fraction reported.

<table>
<thead>
<tr>
<th>Author (Reference)</th>
<th>Year of Publication</th>
<th>Number of Patients</th>
<th>Range of Dose/Fraction (cGy)</th>
<th>Total Dose (cGy)</th>
<th>Control by Radiotherapy</th>
<th>Successful Surgical Salvage</th>
<th>Incidence of Late Major Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fayos (28) 1975</td>
<td></td>
<td>127</td>
<td>185-216</td>
<td>6100-6500</td>
<td>90%</td>
<td>not reported</td>
<td>none</td>
</tr>
<tr>
<td>Olszewski et al (29) 1985</td>
<td></td>
<td>137</td>
<td>180-225</td>
<td>5600-7000</td>
<td>80%</td>
<td>22/27</td>
<td>not reported</td>
</tr>
<tr>
<td>Schwaibold et al (6)* 1988</td>
<td></td>
<td>28</td>
<td>200</td>
<td>6600</td>
<td>100%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Cellai et al (30) 1990</td>
<td></td>
<td>155</td>
<td>180-200 (5X weekly) 300 (3X weekly)</td>
<td>6600-7000</td>
<td>80%</td>
<td>16/31</td>
<td>4.5% permanent tracheostomy</td>
</tr>
<tr>
<td>Krawczyk et al (31) 1991</td>
<td></td>
<td>77</td>
<td>150-226</td>
<td>5500-7020</td>
<td>81%</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Small et al (32) 1992</td>
<td></td>
<td>135</td>
<td>180-280</td>
<td>5400-7000</td>
<td>89%</td>
<td>8/11</td>
<td>not reported</td>
</tr>
<tr>
<td>Rudoltz et al (8)* 1993</td>
<td></td>
<td>70</td>
<td>200-220</td>
<td>6400</td>
<td>87%</td>
<td>not reported for 200 cGy group</td>
<td>1% tracheostomy</td>
</tr>
</tbody>
</table>

*Data for additional dose group(s) from this study appear in other tables.

Toxicity

Data on acute toxic effects were not collected routinely and were mentioned in only nine of 30 case series reviewed for this report. Chronic toxic effects were also irregularly reported (Tables 2 to 6). Laryngeal edema was mentioned by some authors, but this was difficult to quantify and compare across reports. Those authors who described complications consistently reported the permanent tracheostomy rate. There did not appear to be a relationship between tracheostomy rates and either dose per fraction or total dose for the various fractionation courses, with a level of 1% or less being described.

A randomized trial by Teshima et al (3) detected significantly more acute mucosal reactions (p<0.05) and persistent arytenoid edema (p<0.02) with a radiation field size of 6X6 cm² compared with a radiation field size of 5X5 cm², when 6000 cGy was given in 30 fractions over six weeks.
Randall et al (27) reported unacceptable toxicity rates in 71 patients given 333 cGy fractions three times weekly to 60 Gy in six weeks using a single field. There were moderate or severe acute reactions of hoarseness, laryngeal edema and dermatitis in 58%, 19% and 29% of patients, respectively. Chronic complications included moderate or severe laryngeal edema in 10% of patients. Two of seven patients undergoing surgical salvage had severe post-operative complications.

Voice Quality
Quality of voice after radiation treatment was reported for some of the studies listed in Tables 2 to 5, although results were not usually reported separately for T1 and T2. The methods used to assess voice quality were not generally well described.

The proportion of patients reported to have poor quality of voice after radiotherapy varied among the four reports of patients treated with 200 cGy per fraction: 3% of patients in the study by Pelliteri et al had voices that were “harsh but intelligible” (16); 8% in the study by Mantravadi et al developed recurrent hoarseness due to edema of the vocal chords and/or arytenoids (12); 14% in the study by Sinha had poor voice (14); and 13% of 20 patients who received a speech pathology evaluation in the study by Morris et al were judged to have an impaired voice (18).

Voice quality was discussed in two reports of patients treated with doses per fraction between 200 and 300 cGy. Thirty-seven percent of patients who returned for follow-up assessment 24 months or more after treatment with 230 cGy four times a week were rated as having mild or intermittent hoarseness, and one patient had persistent hoarseness due to necrosis of the arytenoid in the study by Luk & Castro (22). Kelly et al (25) reported that 89% of patients had an improvement in voice quality after a dose per fraction of 240 cGy with 73% returning to normal voice.

Moderate hoarseness was reported by Randall et al as a long-term effect of radiotherapy for 16% of patients receiving 333 cGy three times a week (27).

V. INTERPRETIVE SUMMARY
The quality of the current evidence concerning the optimum dose and fractionation schedule for radiotherapy treatment of T1 N0 glottic larynx is poor; the vast majority of clinical papers are retrospective reviews of case series from single institutions. Accepted schedules are based on the delivery of a radical radiation dose with a clinically acceptable complication rate. There is no evidence for the superiority of any one treatment schedule. Excessive toxicity was reported by Randall et al (27) with 333 cGy fractions three times weekly to 60 Gy in six weeks using a single field.

A four-week course of treatment appears to be safe and effective, and is currently given at four of the eight Cancer Care Ontario Centres and at the Princess Margaret Hospital. A report of the Princess Margaret experience by Warde et al (2) has shown results equivalent to other dose and fractionation schedules.

VI. ONGOING TRIALS
No relevant ongoing studies were identified.

VII. OPINIONS OF THE HEAD AND NECK CANCER DISEASE SITE GROUP
Areas of discussion at DSG meetings included: 1) whether or not a recommendation could be made based on the available evidence, 2) the need to consider overall local control rates (i.e., control with radiotherapy and salvage surgery), rather than rates achieved by radiotherapy alone, 3) how patient perspectives could influence evaluation of radiation schedules, 4) the need to consider both acute and late toxic effects, and 5) the relative costs of different radiation schedules. The impact of dose and fractionation schedule on quality of voice was identified as an issue of potential concern to clinicians and patients; a summary of the evidence related to this question was added to the report.
The DSG concluded that in the absence of published evidence, a treatment decision could be based only on other factors such as current practice, patient characteristics, and patient convenience. The majority of DSG members agreed that a four-week course of treatment is supported by a large body of experience within Ontario and appears to provide satisfactory tumour control with minimal patient inconvenience. However, it was anticipated that some centres would be reluctant to change from a five-week to a four-week course because of concerns that they may not maintain high tumour-control rates. Randomized trials will be required to further advance knowledge on this topic.

VIII. JOURNAL REFERENCE

IX. ACKNOWLEDGEMENTS
The Head and Neck Cancer Disease Site Group would like to thank Dr. I Hodson for taking the lead in drafting and revising this evidence summary and for taking the lead in updating this evidence summary.

For a full list of members of the Head and Neck Disease Site Group, please visit the Cancer Care Ontario website at [http://www.cancercare.on.ca/](http://www.cancercare.on.ca/).
REFERENCES